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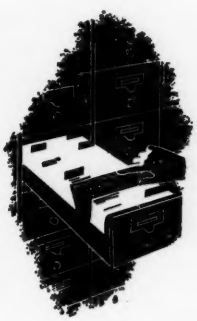

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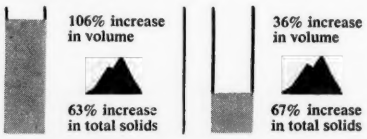

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LABORATORY AND CLINICAL STUDIES ON ERYTHROMYCIN*

THOMAS H. HAIGHT, M.D.,† AND MAXWELL FINLAND, M.D.‡

BOSTON

ERYTHROMYCIN is a new antibiotic produced by an organism that was originally isolated from a soil sample collected on the island of Panay in the Philippines and identified on the basis of its morphology, cultural characteristics and physiology as a strain of *Streptomyces erythreus* (Waksman). The production and some of the chemical and biologic characteristics of this antibiotic have been reported by a group of workers from the Lilly Research Laboratories.§ When extracted with suitable reagents from the filtrate of properly grown cultures of the organism, the antibiotic is obtained in crystalline form as a basic compound that is grayish white, is soluble in water to an extent of about 2 mg. per cubic centimeter but is highly soluble in alcohols and in a number of other organic solvents. Its empirical formula is given as $C_{34-36}H_{60-68}NO_{11-14}$, and its molecular weight is estimated to be about 725.

The results of in vitro tests as reported by these workers showed that gram-positive organisms, including strains of *Micrococcus pyogenes, var. aureus*, that were resistant to other antimicrobials, were highly sensitive, being inhibited by concentrations of less than 1 microgm. per cubic centimeter; strains of some gram-negative organisms, such as Neisseria, Hemophilus and Brucella, and certain mycobacteria were also sensitive, and were inhibited by 6 microgm. or less per cubic centimeter. Resistance of staphylococci to this agent was found to develop at about the same rate as resistance to penicillin. In vivo protective activity was said to parallel in vitro activity and to be related to the blood levels of the agent. Preliminary studies also showed some activity against lymphogranuloma and mouse-pneumonitis viruses and rickettsias growing in egg embryos; in vitro and in vivo activity against *Endamoeba histolytica*; and activity against *Spirocheta novyi* (*Borrelia novyi*), *Trichomonas vaginalis* and oxyurids in mice. The antibiotic was found to have a low order of toxicity when given to mice orally, subcutaneously or intraperitoneally and to dogs by mouth. It was readily detected in blood, urine, feces and cerebrospinal fluid after oral administration in dogs; the peak blood level in that animal was reached in one hour, and the drug could be detected in blood for eight hours. Encouraging preliminary results were obtained in patients with hemolytic-streptococcus and pneumococcal infections from oral treatment with this antibiotic.

Because the early results obtained by these workers seemed favorable and encouraging,¶ and particularly because erythromycin might prove useful in the treatment of staphylococcal infections, additional laboratory studies were undertaken at the Thorndike Memorial Laboratory and a clinical trial in suitable cases, as they became available, was also started. A brief summary of some of the results of these laboratory studies and of the initial clinical observations is presented in this paper.

LABORATORY STUDIES||

Some of the observations of McGuire et al.§ were confirmed and extended and a number of additional studies on the properties and antibacterial action of erythromycin were carried out. Details of the data and methods will be reported elsewhere, but some of the significant findings will be summarized here.

Stability

Sterile solutions of erythromycin in broth in both high (2000 microgm. per cubic centimeter) and low (2 microgm. per cubic centimeter) concentrations were found to retain their activity essentially unimpaired when stored for eight weeks either at 4°C. or in the frozen state at −25°C. At room temperature (±25°C.) there appeared to be some deterioration during the first week but not in the en-

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§McGuire, J. M., et al. Ilotycin, new antibiotic. *Antibiotics & Chemotherapy* 2:281-283, 1952.

¶The data were first made available to us through the kindness of Dr. J. W. Smith, of the Lilly Research Laboratories, who provided us with generous supplies of erythromycin. The trade name adopted for this antibiotic by Eli Lilly and Company is "Ilotycin."

||We are indebted to Clare Wilcox and Marilyn K. Broderick for technical assistance throughout these studies and to Marion E. Lamb and A. Kathleen Daly for isolation and identification of many of the strains.

suing seven weeks, whereas at 37°C. the activity of both solutions began to decline on the fourth day and deterioration continued progressively thereafter. Heating to 60°C. for five minutes had no demonstrable effect, but there was some loss of activity after fifteen minutes at that temperature; a similar loss of activity was noted when solutions were heated to 100°C. for fifteen minutes, but longer exposures at this temperature resulted in considerable inactivation.

Effect of pH, Filtration, Size of Inoculum and Various Chemical Substances

Erythromycin was found to be most active in a moderately alkaline medium; the sensitivity of a test strain increased progressively with increases in the level of pH from 5.5 to 8.5 (about tenfold with each pH unit). Filtration of a solution in broth through Seitz or Berkfeld filters resulted in only slight loss of activity. The size of the inoculum, within a fairly wide range, had no great effect on the sensitivity of test organisms, either in broth-dilution tests or on antibiotic-containing agar. A variety of substances known to affect the activity of penicillin or streptomycin did not influence the activity of erythromycin when they were used in a wide range of concentrations; the substances tested were sodium chloride, glucose, sodium thioglycollate, cysteine hydrochloride, semicarbazide, urea, glutamic acid, para-aminobenzoic acid, folic acid, penicillinase and serum. Erythromycin-resistant strains of gram-negative bacilli that grew profusely on the surface of agar containing the antibiotic did not produce any erythromycin-inhibiting substance.

TABLE 1. *Sensitivity of 920 Strains of Bacteria to Erythromycin.**

ORGANISM	NO. OF STRAINS TESTED	MINIMUM COMPLETE INHIBITING CONCENTRATION	
		RANGE	FOR TWO THIRDS OF STRAINS
		microgm./cc.	*microgm./cc.*
Pneumococcus, various types	58	0.02–0.09	0.04
Hemolytic streptococcus†:			
Group A	50	0.02–0.19	0.04
Group B	14	0.04–0.39	0.19
Group C	21	0.04–0.78	0.19
Group D	24	0.02–3.12	1.56
Group E	2	0.04–0.09	0.09
Group F	4	0.02–0.04	0.04
Group G	20	0.01–0.19	0.09
Endocarditis strains†:			
Alpha streptococcus	10	0.02–3.12	0.39
Streptococcus mitis	3	0.09–3.12	3.12
Streptococcus sanguis	7	0.02–0.09	0.04
Streptococcus faecalis	4	1.56–3.12	3.12
Staphylococcus aureus	614	0.01–1.56	0.39
Corynebacterium diphtheriae	12	0.39–3.12	1.56
Gonococcus	8	0.04–0.39	0.39
Meningococcus	5	0.19–1.56	0.78
Haemophilus influenzae	15	0.78–3.12	1.56
Haemophilus hemolyticus	6	0.78–3.12	1.56
Escherichia coli	10	100 or more	100
Aerobacter aerogenes	6	200 or more	>200
Klebsiella pneumoniae	7	100 or more	>200
Proteus vulgaris	4	>200	>200
Pseudomonas aeruginosa	16	200 or more	>200

*The tests were done by a plate-dilution method.

†Most of the specific strains of hemolytic streptococci were obtained from Dr. Rebecca Lancefield, Dr. Lowell Rantz and Dr. Harry A. Feldman. The strains of *Streptococcus mitis, sanguis* and *faecalis* were obtained from Dr. Leo Loewe.

Mode of Action

Growth curves of a strain of hemolytic streptococcus in broth containing various concentrations of erythromycin indicated that within certain limits the rate at which the organisms were killed increased with increases in the concentration of the antibiotic. The time required to kill the test organisms was proportional to the number of organisms (per cubic centimeter) originally present. The antibiotic was active against rapidly multiplying organisms.

Sensitivity of Pathogenic Bacteria

To date, 920 strains of bacteria, most of them recently isolated from patients with various infections, have been tested for sensitivity to erythromycin by a plate-dilution method. The results are summarized in Table 1. Pneumococci and Group A hemolytic streptococci were the most sensitive, the other streptococci, staphylococci and Neisseria being somewhat less sensitive, as were also the strains of hemophilus and of diphtheria bacilli. Coliform bacilli, proteus and pyocyaneus organisms were all quite resistant. Naturally occurring strains of staphylococci resistant to erythromycin have not been encountered thus far.

Comparison with Other Antibiotics

Many of these strains have also been tested for sensitivity to other antibiotics, particularly to penicillin, aureomycin and terramycin. On a weight basis, the erythromycin was essentially similar in its activity to penicillin; it was more active than the broad-spectrum antibiotics against the gram-positive organisms, less active against the gram-negative coliform bacilli and about equally active against strains of hemophilus.

Development of Resistance in Vitro

Attempts were made to increase the resistance of several strains of initially sensitive organisms by serial subcultures on agar containing progressively increasing concentrations of erythromycin. Strains of staphylococci and a strain of enterococcus increased in resistance rapidly so that they grew on 100 microgm. per cubic centimeter after three to five transfers. A strain of pneumococcus required twelve transfers at forty-eight-hour intervals to reach the same level of resistance, whereas a Group A hemolytic streptococcus and a strain of *Str. viridans* increased in resistance only slightly after twenty subcultures on erythromycin agar.

Absorption and Excretion

Specimens of blood and urine were obtained for assay from patients under treatment with erythro-

mycin and from others with normal renal function who were given individual doses. In general the blood levels on the small doses used early in this study varied widely in different patients but some activity could usually be demonstrated in the plasma in almost every case. There was a rough correlation between the maximum blood levels and the dose of drug ingested. The peak blood levels were found between one and two hours after a dose, and there was a rapid decline thereafter so that activity could usually not be demonstrated after four or six hours. Only small amounts were recovered from the urine. Further studies on this aspect are in progress.

Clinical Observations*

At the time of this writing, treatment has been completed in 41 patients; these were regular admissions to the wards or outpatient clinics of the Boston City Hospital. More than two thirds of the patients were treated for either pneumonia or hemolytic-streptococcus infections; none of them had received any antimicrobial therapy for this infection before erythromycin was started. Some of the remaining patients, however, were given erythromycin only after it had become clear from the clinical course or bacteriologic findings, or both, that they were not responding to the agents that they had been receiving. Still under observation and treatment at this and other hospitals are 4 additional patients with severe staphylococcal infections who have shown initially favorable responses. The results of the clinical and laboratory findings in the 41 patients whose treatment has been completed will be summarized briefly; the types of cases, the range of the total dose used and a rough estimate of the clinical and bacteriologic response to treatment are shown in Table 2. All doses were given by mouth; the dosage regimens were mainly experimental and depended in part on the dosage forms available, and they were altered as experience was acquired. The various dosages actually employed are listed in Table 3. Larger doses are being used in the patients with staphylococcal infections currently under therapy.

*We are indebted to many members of the hospital staff for permission to study these cases. The patients with scarlet fever and the diphtheria carriers were studied with the assistance and co-operation of Dr. Henning Poulsen, assistant resident physician at the South Department of this hospital; the cases of gonorrhea and nonspecific urethritis were studied with the assistance and co-operation of Drs. Linus Cave and Marcel Belanger and Mrs. Helen W. Trousdale.

Effects in Pneumonia

Of the 16 cases of pneumonia, 15 were due to pneumococci of various common specific types, and in the other no specific inciting pathogen could be isolated. Erythromycin was started in the pneumonias between the first and the fourteenth day after the onset, but in most cases it was begun on or before the fourth day. The dose in the first 8 patients was 200 mg. initially, followed by 100 mg. every three hours; 5 patients received 250 mg. initially and 125 mg. every three hours; 2 others were given 200 mg. every three hours, and 1 received 250 mg. every three hours. Treatment was continued for two to fourteen days (average six-and-one-half days); the total dose per patient was 1.4 to

Table 2. *Summary of Clinical Results in Patients Treated with Erythromycin by Mouth.*

Disease	No. of Patients	Total Dose	Result: Good	Result: Indifferent	Result: No Effect
		gm.			
Pneumonia (16 cases):					
Pneumococcal, bacteremic	4	1.4–14.0	2	2	0
Pneumococcal, nonbacteremic	11	2.8–16.8	11	0	0
Etiology not determined	1	3.0	1	0	0
Streptococcal infections (13 cases):					
Pharyngitis	2	3.0–5.5	2	0	0
Acute follicular tonsillitis	4	2.5–12.6	4	0	0
Scarlet fever	7	7.2–13.5	4	2	1
Staphylococcal infections:					
Pharyngitis	1	6.0	1	0	0
Enteritis	1	3.4	1	0	0
Diphtheria (carriers)	3	14.0–17.0	3	0	0
Gonorrheal urethritis	4	1.0–3.0	2	0	2
Nonspecific urethritis	3	2.4–5.0	0	0	3
Totals	41	....	31	4	6

Table 3. *Dosage Regimens of Erythromycin.*

Schedule	Dose	No. of Patients
A	200 mg., then 100 mg. every 6 hours	2
B	200 or 250 mg., then 100 or 125 mg. every 3 hours	23
C	400 or 500 mg., then 200 or 250 mg. every 3 or 4 hours	12
D	Schedule B for 2 to 4 days, followed by Schedule C	4

Table 4. *Effect of Erythromycin on Bacteriologic Findings in 15 Patients with Pneumococcal Pneumonia.*

Bacteriologic Findings	No. of Patients
Blood cultures positive before treatment	4
Blood cultures positive after treatment was started	0
Pneumococci in sputum cultures before treatment	15
All sputum cultures negative for pneumococci:	
1 day after treatment was started	9
2 days after treatment was started	5
3 days after treatment was started	1

17.0 (average 6.9) gm. Most of the patients received 5 to 8 gm. in four to eight days. None of the patients received other antimicrobial agents for these infections.

The bacteriologic results in the pneumococcal pneumonias are summarized in Table 4. Four of the patients had positive blood cultures for pneumococcus before treatment was begun; all blood cultures taken in these patients after erythromycin was started were negative. Pneumococci could no longer be cultured from the sputum after the first case. The 11 nonbacteremic patients all showed a rapid and favorable course, with subsidence of fever and acute symptoms within forty-eight hours. The patient from whom pneumococci were not isolated manifested rapid symptomatic improvement and became afebrile within twenty-four hours. Cold agglutinins did not develop, and it is most likely that this was a case of pneumococcal pneumonia.

The course and relevant findings in 3 patients with pneumococcal pneumonia are shown in Figure 1. Two of these patients demonstrated a rapid drop

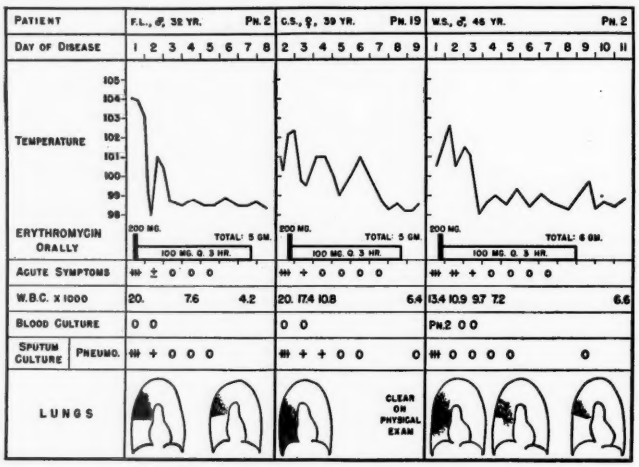

FIGURE 1. *Results of Oral Administration of Erythromycin in Pneumonia.*

day of erythromycin therapy in 9 of the 15 patients; they were still present after the first day but could not be isolated on the second day or later in 5 patients, and in no case could pneumococci be cultured from sputum on or after the third day of treatment.

The clinical effects in the 16 patients with pneumonia were essentially similar to those observed with sulfadiazine, penicillin or the broad-spectrum antibiotics. Of the 4 bacteremic patients, 3 had fever for two to five days after erythromycin treatment was started; the fever then gradually subsided, and the signs and symptoms of active infection cleared progressively. One of these patients had pneumococcal empyema demonstrated before treatment was begun; although this patient was progressing favorably, he had a massive hematemesis and died. Autopsy revealed a large gastric ulcer. In the fourth patient treatment was begun after she had been acutely ill for two weeks; she died on the second day, and autopsy disclosed an extensive, purulent pericarditis. Pneumococci could not be obtained from cultures of the purulent pericardial fluid, nor from the lungs and cardiac blood in this in temperature, and all showed prompt improvement after the institution of erythromycin therapy. The number of pneumococci in the sputum declined promptly and then cleared in all patients. No specific organisms have been found consistently to replace the pneumococci in the sputum, and in no case has hemolytic *Staphylococcus aureus* been observed after therapy. The white-cell count fell progressively to normal in all cases, generally running a similar course to the temperature and acute symptoms. Serial x-ray films were taken in each case, and in the 14 patients who survived, x-ray evidence of clearing of the pneumonic process was noted, although 2 patients required three or four weeks for complete clearing.

Effect in Streptococcal Infections

The results of erythromycin therapy in the 13 patients with acute hemolytic-streptococcus infections are summarized in Table 2. The first 3 adults with pharyngitis or acute follicular tonsillitis received an initial dose of 200 mg. and 100 mg. every three hours; in 1 of these patients the dose was increased to 200 mg. every three hours on the third

day. The 3 subsequent patients were treated with 500 mg. initially and 250 mg. every four hours. Treatment was given for an average of 9 gm. in five-and-one-half days. All these patients showed good responses, with rapid decline of temperature, decrease in symptoms and subsidence of all signs of active infection within twenty-four to seventy-two hours. The streptococci cleared rapidly, often within twelve or twenty-four hours, and after the regimen was increased to the larger doses, most of the patients were free of causative organisms after the third day on erythromycin.

TABLE 5. *Effect of Erythromycin on Bacteriologic Findings in 13 Patients with Hemolytic-Streptococcus Infections.*

CULTURES FOR HEMOLYTIC STREPTOCOCCI	NO. OF PATIENTS
Blood cultures positive before treatment	0
Throat cultures positive before treatment	13
Repeated throat cultures negative after:	
1 day of treatment	3
2 days of treatment	4
6 days of treatment	1
8 days of treatment	1
15 days of treatment	1
16 days of treatment	1
18 days of treatment	1
Throat culture positive after 23 days of treatment	1

The 7 children with scarlet fever showed a somewhat less consistent response. The dose used at first was 100 or 125 mg. every six hours, and later those amounts were given every four hours. Treatment was continued for an average of 9.6 gm. in eleven days. The disappearance of the streptococci from the throat cultures occurred less regularly in these patients, and it was not uncommon to find isolated or persistently positive cultures while the patient was still on therapy. After the dose was increased there was some improvement, but 3 patients required treatment for fifteen, sixteen and eighteen days, respectively, before cultures became negative. One patient had a positive culture on the twenty-third day. The results of the bacteriologic findings in the streptococcal infections are summarized in Table 5.

Clinically, the children with scarlet fever, like the adults with pharyngitis and tonsillitis, all responded dramatically. The fever subsided within twenty-four to forty-eight hours, the rash ran a natural course of one to five days, and all other evidence of active infection was generally gone within two to five days. The white-cell counts in all these cases paralleled the clinical course. The course and relevant findings in 3 patients are shown in Figure 2.

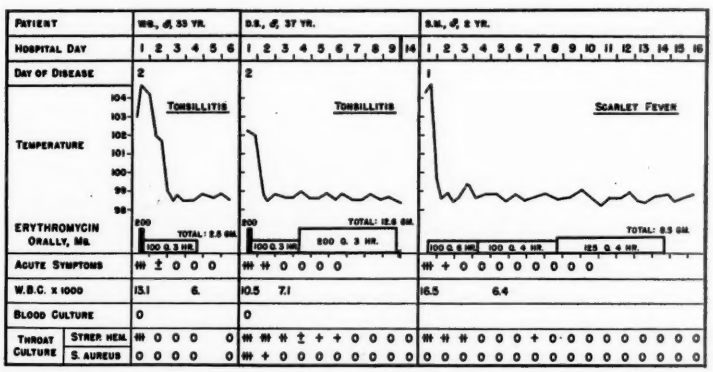

FIGURE 2. *Results of Oral Administration of Erythromycin in Hemolytic-Streptococcus Infections.*

Effect in Miscellaneous Cases

Erythromycin was used in the treatment of 4 patients with acute gonorrheal urethritis; the gonococcus was isolated in each case before therapy. Two of these patients showed symptomatic and bacteriologic clearing on a course of 1.0 gm. given in one day; in 2 others, however, the infection did not clear on this dose or when they were re-treated with 2.0 gm. on the second day. The latter 2 patients still had positive cultures and were therefore given 300,000 units of procaine penicillin intramuscularly, to which they responded. Three patients with acute nonspecific urethritis showed no response in symptoms nor in the character or quantity of discharge; 1 of them received 5 gm. in three days; the other 2 received 2.4 gm. in two days.

Three patients who were carriers of virulent diphtheria bacilli and had persistently positive cultures while on penicillin therapy were given erythromycin, 250 mg. every six hours, to a total of 14 to 17 gm. in twelve to eighteen days. The organisms were cleared from the throat cultures of each patient within six days, and in 1 negative cultures were obtained after the first day. At least three negative

cultures at intervals of one to three days were obtained in each case after the end of treatment.

Two patients with staphylococcal infections were treated. A young student nurse with infectious mononucleosis and a severe superimposed pharyngitis with pure cultures of *Staph. aureus*, which had not responded to previous penicillin therapy, showed prompt clearing of the organisms from her throat and a parallel improvement in the throat symptoms. In a young Negro who had received terramycin therapy for pneumococcal pneumonia severe enteritis associated with persistently positive stool cultures for staphylococci developed. Large quantities of paregoric and bismuth were necessary for symptomatic therapy of the diarrhea, but when all therapy was omitted and erythromycin was given, the stools promptly became soft and formed, no staphylococci could be found in any subsequent stool cultures, and the patient made a good clinical response.

Two additional patients are now under therapy with erythromycin for staphylococcal infections at this hospital. In 1 of them erythromycin was given for a meningitis that had not previously responded to massive doses of penicillin intramuscularly and later aureomycin intravenously. The initial response was favorable, the cerebrospinal fluid was cleared of organisms for the first time, and clinical improvement followed. The second patient still under treatment is an elderly woman who had had multiple operations for various abdominal conditions; erythromycin was given for a staphylococcal bacteremia, which had not responded to penicillin or aureomycin. The patient was almost moribund when erythromycin was started; however, except for one obtained on the first day after therapy, all blood cultures have been sterile subsequently, and the patient has shown striking improvement. Both patients are progressing favorably.

Two patients with staphylococcal endocarditis were treated with erythromycin by mouth at other hospitals after they had failed to respond to prolonged therapy with full doses of other antibiotics. Only minor improvement occurred initially in 1 of these patients on increasing doses up to 500 mg. every three hours. When this dose was reached, however, intractable vomiting occurred, the fever rose again to high levels and the patient's condition deteriorated progressively. The erythromycin was stopped, and he died a few days later. In the second patient 3 gm. daily for six days (0.5 gm. every four hours) and 4 gm. daily for four more days (0.5 gm. every three hours) were well tolerated; fever and bacteremia, however, persisted. In both these patients 2 gm. of streptomycin was given daily by the intramuscular route throughout the period of erythromycin therapy because that was the only widely used antibiotic to which the organisms were still sensitive in any degree. In spite of this, the staphylococci cultured from the blood at the end of the period of erythromycin therapy had increased markedly in resistance to that agent.

Untoward Effects

No toxic symptoms of any sort attributable to erythromycin have been observed in the patients thus far studied, except the vomiting in 1 patient as mentioned in the preceding paragraph.

Summary and Conclusions

The results of laboratory and clinical studies with a new antibiotic, erythromycin, are presented. In its antibacterial spectrum, its mode of action and its clinical efficacy in the treatment of the acute infections thus far treated, this new antibiotic appears to be similar to penicillin. However, it is active against penicillin-resistant staphylococci, though not in all cases, and does not seem to be as effective as penicillin in gonorrhea. To date, no toxic effects from oral therapy have been observed, except for vomiting in 1 patient.

Because of the possibility that this agent will be of value in the therapy of certain acute infections resistant to other antibiotics, erythromycin appears to deserve a further clinical trial.

THE EARLY TREATMENT OF PULMONARY TUBERCULOSIS*

COLONEL CARL W. TEMPEL, M.C.,† AND DUMONT CLARK, M.D.‡

DENVER, COLORADO

THE therapy of pulmonary tuberculosis has progressed markedly in recent years. It is desirable, therefore, to review present trends in treatment for the benefit of those not actively engaged in tuberculosis research and in the hospital care of patients. A final pattern of treatment has not yet emerged, but enough has been accomplished so that the physician can offer the patient with newly discovered[1] pulmonary tuberculosis a fairly specific course of therapy for his disease. To this end it is proposed to indicate briefly the place of rest in the treatment of pulmonary tuberculosis; to discuss certain developments in therapy — namely, drug treatment and pulmonary resection; to mention some of the abuses of temporary collapse procedures; and, lastly, to present a plan for the early treatment of the newly discovered case of pulmonary tuberculosis.

REST AND PHYSICAL REHABILITATION

Rest of body and mind remains a fundamental requisite of treatment. In most cases, by the time the tuberculous lesion has been discovered and diagnosed, tuberculin sensitivity has developed. As a result,[2] the tuberculous lesion is frequently involved in caseous necrosis with destruction of more or less lung tissue. Any destructive process, such as a third-degree burn, requires a considerable period of rest to effect healing. Such a situation exists in tuberculosis, in which a destroyed area of lung needs time for healing. Rest is also required to afford the body an opportunity to mobilize its immunization and other mechanisms of defense against infection.[3, 4] Bed rest is best attained in a hospital, where the patient with newly found active tuberculosis should properly be located because of the contagiousness of his disease. A gradual increase in physical exercise is permitted to patients as improvement occurs, and ambulation is usually possible when the disease becomes inactive.

NEW DEVELOPMENTS IN THERAPY

Two new developments in the treatment of pulmonary tuberculosis add materially to the ability of the physician to handle the disease. They are chemotherapy, particularly the combined use of streptomycin and para-aminosalicylic acid (PAS), and resectional surgery of the lung, by means of which a small wedge, segment, lobe or an entire lung may be removed.

TABLE 1. *Two Separate Studies on Development of Resistance of Tubercle Bacilli to Combined Use of Streptomycin and PAS in Human Subjects.**

	Treatment for 120 Days			Total No. of Cases	Negative Bacteriologic Results	Positive Bacteriologic Results		
	Drug	Dose gm.	Method			Total	Sensitive	Resistant†
Series I	Streptomycin and PAS	1 12	Twice weekly Daily	99	59	40	38	2 (5%)
Series II	Streptomycin and PAS	2 12	Every 3 days Daily	95	63	32	32	0 –

*Based on summary discussion of Table XII in Dye.[7]

†Resistance in this study is interpreted as growth of bacilli on 10 microgm. of streptomycin per cubic centimeter of medium equal to growth on control tube.

Antibacterial Substances

There are a number of excellent studies in the literature[5, 6] on the use of antibacterial agents in the treatment of tuberculosis. Undoubtedly, other substances not yet discovered or publicized will be made available in the future. At present the combined use of streptomycin and PAS, administered in proper dosage to patients with tubercle bacilli sensitive to these substances, markedly limits the growth of the invading tubercle bacilli and produces a minimum of toxicity. In addition, since the combined use of streptomycin and PAS defers considerably the development of bacterial resistance (Table 1),[7] these agents can now be administered for periods of four months or longer. It is important early in the treatment of any newly discovered case of tuberculosis to obtain a culture of the tubercle bacillus and to determine its sensitivity to streptomycin

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and PAS. With no exceptions, the patient should be hospitalized while he is undergoing the first course of treatment with streptomycin and PAS. Drug toxicity, although generally slight, is always potentially dangerous. Serious irritation of kidneys, liver, bone marrow, skin or nervous system can occur.

It must be determined that the patient can tolerate both drugs. Because of gastrointestinal irritation, a few patients find it difficult to take PAS, which is given orally. For this reason PAS may be given to the patient before streptomycin therapy

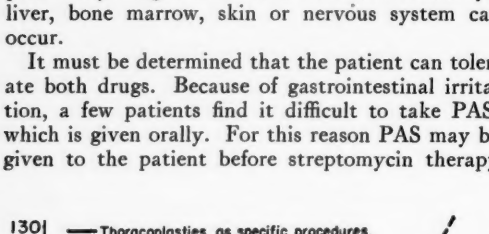

FIGURE 1. *Comparison of Thoracoplasty and Pulmonary Resection During a Five-Year Period at Fitzsimons Army Hospital (Data Supplied by Colonel James H. Forsee, M.C., Chief of Surgical Service).*

is initiated. One gram of PAS (2 tablets)* can be taken three times a day after meals, and the dose increased 1 gm. three times a day until 12 gm. a day is taken. The administration of the drug should be supervised by a nurse until it is throughly established that the patient can and does take the medication. PAS can be given subcutaneously and intravenously,[8] but parenteral use is reserved mainly for emergencies. Only after the drug has been administered satisfactorily for six or seven days should streptomycin therapy be started. Streptomycin is given every third day in the treatment of tuberculous patients at Fitzsimons Army Hospital.[9] If this routine proves confusing to the nursing staff, it can be given twice weekly with equally good results. A rather arbitrary plan has been followed in which an adult weighing under 120 pounds is given 1 gm. of streptomycin or dihydrostreptomycin sulfate intramuscularly as stated above; 2 gm. is given if the patient's weight is over this amount. A blood count and urinalysis are done once weekly for the first month and once or twice a month thereafter. The nonprotein nitrogen of the blood is determined initially and once a month or as indicated until treatment is completed. Evidence of renal insufficiency or severe toxic effects is usually sufficient cause to discontinue treatment.

*Sodium PAS is available in tablet form and may be less irritating than PAS.

Excisional Surgery

Removal of the upper lobe, usually in association with thoracoplasty of the first four or five ribs, and lower-lobe excision, usually followed by temporary paralysis of the homolateral portion of the diaphragm, have been performed in the treatment of pulmonary tuberculosis on a fairly extensive scale for six or seven years.[10-12] Pneumonectomy, along with thoracoplasty, has been a considerably more hazardous procedure than lobectomy and has been done to a much less extent.[13] In the last three or four years when these procedures were performed on patients in whom the tubercle bacilli were sensitive to the effects of streptomycin and to whom streptomycin was administered before, during and after operation, the immediate postoperative results have been very good, showing a low rate of mortality and spread or reactivation of disease.[14] In the past, many new methods of treatment of pulmonary tuberculosis have been enthusiastically proposed. Experience, often bitter, has shown that any new treatment for tuberculosis must be evaluated over a period of at least five years. The late results of resection that has been done after the lesion has been thoroughly stabilized with rest and chemotherapy[15] are almost as good as the early postoperative results. In addition to the good results with lobectomy, Chamberlain and Klopstock[16] have demonstrated that under comparable conditions of operability and streptomycin sensitivity, parts of a lobe can be removed successfully, with consequent preservation of pulmonary function and diminution of chest-wall deformity. On the other hand, a carefully performed thoracoplasty[17, 18] will frequently accomplish all that resection can, except in so-called round lesions or in lesions involving the lower lobes. In addition, thoracoplasty has stood the test of time. It has been indicated that resection[16] has possibly two advantages over thoracoplasty. These are retention of more pulmonary function and less deformity of the chest wall. A thoracoplasty of three, four or five ribs is not very deforming, whereas the usual thoracoplasty done as a specific procedure requires the removal of seven or more ribs and is always deforming. When a thoracoplasty was the only successful surgical procedure available, it had to be used. This situation is no longer true (Fig. 1).

This is not to imply that resection has any considerable advantages over properly selected thoraco-

plasties. Actually, the choice of operation depends to some extent on the training, skill and preference of the surgeon. The only inference to be drawn is that resection in competent hands is rapidly attaining the respectability and responsibility of thoracoplasty. There is, however, another point that should be raised about these two procedures. The plan of treatment (Table 2), which will be given in some detail below, as presented to the new patient includes the possibility of surgery, either pulmonary resection or thoracoplasty. It may be that by the time surgery is indicated, thoracoplasty will be the procedure of choice. It also follows in most tuberculosis hospitals that by the time a thoracoplasty is indicated the average patient will be willing to accept it. A large thoracoplasty, seven ribs or more, usually is not considered until other means of treatment have failed. Early in the course of the disease, however, the patient will generally accept resection more readily than a large thoracoplasty. The fact that the patient will probably accept a plan of treatment with resection, if it is necessary, but might refuse a plan that envisions a major thoracoplasty if other methods fail is a point in favor of resection. As present-day methods of treatment of pulmonary tuberculosis are very effective, it is important for the patient to accept the whole plan, which carries therapy to the point of likely cure with the help of surgery if needed in a minimum of time.

Temporary Collapse

The indications and contraindications for the use of temporary-collapse procedures such as pneumothorax, pneumoperitoneum and phrenic-nerve crush are not discussed in this report. It is mainly to emphasize some of the misuses of these procedures that the present remarks are directed, the most common being the substitution of these measures for bed rest.

In a recent thorough study of artificial pneumothorax, Mitchell[19] has shown that the indications for the procedure are quite limited and that induction of pneumothorax should be preceded and followed by a period of bed rest. Many similar rules are applicable to pneumoperitoneum.[20] Such principles are rather frequently violated by overzealous proponents of temporary collapse. If a satisfactory collapse is obtained, the physician is apt to persuade the patient that maintenance of the collapse is all that is necessary to achieve a cure. This state of affairs is likely to be especially troublesome when the patient, for one reason or another, undergoes treatment by a new physician. The new physician may have difficulty altering the treatment, particularly if he thinks surgery is advisable.

Studies indicate that many new* active, minimal tuberculous lesions will become inactive with rest therapy alone.[21-23] It has been noted in mass chest x-ray surveys[24] that the percentage of cases diagnosed from the roentgenograms as arrested tuberculosis is roughly ten times that of active tuberculosis. Some of these patients with arrested tuberculosis have had treatment, and many of the cases have been wrongly diagnosed in the survey. Regardless of this, there still remains a sizable though undetermined percentage of patients with apparently healed tuberculous chest lesions who have had no treatment for their tuberculosis or, in fact, were entirely unaware that they had the disease. If collapse therapy is given for the treatment of early tuberculous lesions before the trend of the disease is observed, the physician can anticipate marked improvement in many cases within a short time. This advantage is frequently credited to the temporary-collapse procedure rather than to the native resistance of the patient. Lack of ability, even by the most highly skilled phthisiologists, to foretell which case of active tuberculosis will heal without treatment makes therapy necessary for all. Mention is made of the advantage occasionally claimed for temporary-collapse procedures in the treatment of new lesions of pulmonary tuberculosis in order to point out the possible error involved in such an assumption.

*Attention is called to the fact that a "new" lesion, meaning a lesion of recent origin, is to be distinguished from a "newly discovered" lesion, which may or may not be of recent origin.

TABLE 2. *Outline of Plan for the Early Treatment of Active Pulmonary Tuberculosis.*

THERAPEUTIC REGIMEN	DURATION OF SPECIFIC TREATMENT IN HOSPITAL	PERIOD OF HOSPITALIZATION TO DATE OF DISCHARGE
	mo.	*mo.*
1. Study of new patient and his disease (diagnosis may be established before hospitalization in some patients while others require prolonged study to evaluate nature and stability of pulmonary lesion)	0–4	—
2. Chemotherapy (emergency conditions such as acute tuberculous pneumonia and miliary tuberculosis require immediate chemotherapy)	4–8 (or longer)	—
3. Rest regimen (rest therapy is continuous for all patients from admission to discharge, ambulation being permitted as disease becomes inactive)	10–18	10–18
4. Temporary-collapse procedures (pneumothorax or pneumoperitoneum, usually preceded by at least 4 months of chemotherapy)	6–18	12–24
5. Surgery, excisional or thoracoplasty (preoperative period varies with stability of lesion)	—	12–36

PLAN FOR EARLY TREATMENT

It is extremely important to offer the new patient with tuberculosis a plan (Table 2) for the treatment of his disease. The plan should envisage treatment to the point of eventual inactivity or "cure." The patient then has something around which he can reconstruct his future. The plan must be presented positively. This does not mean that it will be rigid. On the contrary, when the course of the disease under treatment does not follow the usual pattern, ade-

quate provision for an alternate plan of management should be made. The details of therapy are not emphasized, since individualization is required for the various types of disease.

Such a plan of treatment represents the therapeutic principles as practiced at Fitzsimons Army Hospital. It is based on a continuing study of patients who have been successfully treated. In 1951, 414 patients were discharged from Fitzsimons with "inactive disease" (National Tuberculosis Association Standards, 1950[25]) and with maximum hospital benefit. The 414 patients represent approximately a third of the total tuberculous patients discharged in 1951. Not evaluated are those who died, those who left against medical advice and disabled military personnel, who were transferred to Veterans Administration hospitals without completing treatment. A more exhaustive study of these discharges will be covered in a later report. The following procedures were used on the 414 successfully treated patients, all but 28 of whom had pleural or pulmonary tuberculosis:

Rest therapy and temporary collapse. Ninety-three patients received bed rest only. Three additional patients had temporary collapse as well. Forty-five of the patients in this group had pleurisy with effusion, a condition now frequently treated with chemotherapy. Three patients had glandular tuberculosis only. Thirty-seven of the remaining patients had negative sputums. The other 8 patients had positive sputums, but conversion to negative occurred quickly and the response to rest treatment was also satisfactory.

Chemotherapy alone. One hundred and ten patients had rest therapy (which is maintained on all hospital patients) and chemotherapy.

Chemotherapy and temporary collapse. One hundred and thirty patients were treated with chemotherapy and temporary collapse. Of this number, 114 were discharged while still receiving pneumoperitoneum; 5 were receiving pneumothorax; and 11 had received phrenic-nerve crush.

Chemotherapy and surgical procedures. Seventy-eight patients had surgical treatment and all but 5 had chemotherapy. Fifty-two of these patients had excisional operation; 19 had thoracoplasty, and 7 had other surgical procedures.

It can be seen from this study that most patients receive chemotherapy. The relatively high percentage of patients who received surgical treatment is in contrast to former practice at Fitzsimons and other tuberculosis hospitals. The time required to accomplish the results referred to above was evaluated and incorporated in the plan of treatment.

The first consultation after a diagnosis of active pulmonary tuberculosis has been established is of great importance to the patient, who is fearful, rather overwhelmed, but also most anxious to know how long it will take to effect a cure. To allay his fears and answer his questions a basis of friendship and trust between him and his doctor needs to be established. A number of eminent physicians[26] down through the years have declared that friendship between patient and doctor is a most important and fundamental relation. When it is developed there are few emotional or nervous problems of the patient that the physician cannot handle. In addition, before the physician can adequately answer his patient's questions he must discuss with him certain basic facts about tuberculosis. For the physi-

TABLE 3. *Treatment of Active Pulmonary Tuberculosis Based on an Estimate of Lung Disease.*

CLASSIFICATION OF PULMONARY LESIONS*	MEDICAL TREATMENT STREPTOMYCIN-PAS REGIMEN	TEMPORARY COLLAPSE	SURGICAL TREATMENT THORACOPLASTY	PULMONARY RESECTION
New patient	Bed rest begun for all patients; other measures started on tentative classification.			
Unclassified lesions				
Recently developed or new disease				
Reversible lesions (chiefly exudative) ...	Short course	X†		
Irreversible (necrotic or caseous)	Long course	X		
Reversible and irreversible	Long course	X		
Long-standing or old disease				
Reversible (chiefly nodular tubercle, exemplified by chronic disseminated nodular tuberculosis)	Short or long course	X		
Irreversible				
Localized (tuberculoma)	Prophylactic			X
Nonlocalized (fibrocavernous)	Short or long course		X	X
Mixed new and old disease				
Reversible and irreversible	Short or long course	X	X	X
Miliary tuberculosis				
(Acute disseminated tuberculosis).....	Special long course			
Healed lesions — apparently cured				
(Fibrocalcific)	No treatment			

*Based primarily on serial chest roentgenograms.

†X indicates therapeutic measure having greatest application.

cian's immediate purposes these include the infectious and contagious nature of the disease, its tendency to destroy infected tissues, the necessity for rest, the minimum time needed to effect a cure, and the inability to forecast all the measures that may be necessary to remedy the condition. As a recurring theme of this discussion the physician should emphasize the uncertain nature of a so-called cure of tuberculosis.

When the patient better understands the nature of tuberculosis, he will recognize the necessity for a thorough evaluation of his own disease (Table 3). As this study proceeds the various therapeutic efforts can be discussed with him. Generally speaking, the combined use of streptomycin and PAS is the first specific procedure to be employed. The lesions to be treated should include minimal as well as far advanced and most cases of pleurisy with effusion. It should be noted that the duration of chemotherapy as outlined in Table 2 varies from four to eight months or more. Long courses of chemotherapy[27, 28] are being used more often. The employment of chemotherapy in the treatment of pulmonary tuberculosis in which the tubercle bacillus has not been found by smear or culture is a matter of considerable responsibility. Its use requires the opinion of one well versed in the diagnosis and handling of the disease. The remainder of the steps in the plan of treatment follow in the order of their necessity.

It can be seen from a study of Table 2 (Regimen No. 3) that the shortest time in which an inactive lesion can be achieved is approximately ten months, including the period of observation and four months of chemotherapy, all of which time the patient is on rest therapy. Hospital care is continued until the lesion has been stabilized without evidence of cavitation for a minimum of six months. Rehabilitation procedures are begun as soon as the patient is relatively symptom free. If he is a good candidate for temporary collapse, this can be given after two to four months of chemotherapy. It may then be possible for him to leave the hospital after another eight months to continue the collapse treatment as an outpatient. The successful pneumothorax or pneumoperitoneum can be discontinued two or three years after induction. A few patients who require resection may leave the hospital within twelve months. This group includes chiefly those with well localized or solitary lesions that can be treated surgically after a few weeks of chemotherapy. Most patients require a longer period of hospitalization — perhaps eighteen months or two years — mainly because of the additional time required to prepare them for surgery. It should be stated that an apparently radical surgical procedure of pulmonary excision performed early in the course of the disease may prove to be the most conservative procedure in the long run. It is the morbidity and economics of tuberculosis rather than the mortality from the disease that now require attention. A usual sound rule of therapeutics is to let well enough alone. Too often when this is done in the treatment of tuberculosis the patient returns to the hospital over and over again with a new breakdown of his lesion. In an effort to prevent repeated breakdowns, the present tendency is to give the patient maximum treatment at the first opportunity.

An estimate of lung disease[29] as judged by serial chest roentgenograms is necessary for the sound management of pulmonary tuberculosis (Table 3). The clinicopathologic lesions as described are divided into ten groups. A short explanation of these terms is offered as a help in understanding their significance.

Unclassified lesions. The new patient falls into this group on admission to the hospital unless classified by previous clinical studies, serial roentgenographic examination or strong clinical evidence. Strict bed rest is started. Bed rest is continued with modifications until the patient leaves the hospital. Great individualization is required in applying treatment.

New reversible lesions (exudative and nodular tubercles). Rest alone may prove to be an adequate form of treatment, but the present tendency is to treat all such cases with chemotherapy (four months or more) supplemented by temporary collapse as required.

New irreversible lesions (necrotic or caseous). Management of these lesions is the same as that for new reversible lesions except that extensive disease, particularly acute caseous pneumonia, constitutes a medical emergency and the prompt initiation of a long course of chemotherapy (eight months or more) is indicated. Fibrocaseous or cavernous residua are treated as old lesions after an appropriate period of stabilization by medical management, which frequently includes pneumoperitoneum.

New reversible and irreversible mixed lesions (caseous bronchopneumonia). Treatment is the same as that described above for irreversible lesions.

Old disease of a reversible type (best exemplified by chronic disseminated nodular tuberculosis). Short or long courses of chemotherapy often prove effective even though the disease is of many years' duration. Present results favor the use of prolonged courses of drug treatment.

Old localized lesions (tuberculoma). Excision is usually required. A short prophylactic course of streptomycin is given before and after operation. A long course of chemotherapy may be indicated by the findings at surgery.

Old nonlocalized lesions (fibrocaseous cavernous). Thoracoplasty or pulmonary resection is frequently required for persistent cavitary lesions. Rest and chemotherapy, with and without tempo-

rary collapse, often result in negative sputum and small areas of residual disease without cavity. Unless chemotherapy is maintained for a long period (eight months or more), it is probably best to remove dangerous necrotic foci that are sufficiently well localized because the future course of these caseous lesions is unpredictable. Current research on the long-term drug regimens may alter this approach.

Mixed new and old lesions. The new component is usually given first attention. A short or long course of chemotherapy is instituted, with or without temporary collapse as required. The old component may be controlled by the measures prescribed for the new lesions; if not, the treatment is surgical.

Miliary lesions. Special long courses of daily therapy with streptomycin (1 gm.) and PAS (12 gm.) are given. Chemotherapy should be continued six months beyond the period of remission.

Apparently cured lesions (*National Tuberculosis Association Standards*). No treatment is necessary. Periodic examinations including roentgenograms and sputum and gastric studies are required.

The time needed to bring active tuberculosis under control is still a matter of many months. The time factor, however, is no longer so great that it should be a stumbling block in the way of successful treatment. Woodruff[30] stated the situation well when he said that physicians should now treat pulmonary tuberculosis vigorously at the first opportunity with all necessary and available weapons until arrest or cure of the disease is attained. This means "total care, not half care."[31]

Summary

Evidence has accumulated that a large majority of patients with newly discovered pulmonary tuberculosis can be treated successfully with specific measures. Because of this, physicians should acquaint themselves with the measures that are used in treatment. Since the possibility exists of early arrest or cure of the disease, immediate hospitalization is necessary so that total care can be given to the tuberculous patient. Such a policy may materially reduce the number of repeated breakdowns from which many tuberculous patients suffer.

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THE SYNDROME OF IMPENDING HEPATIC COMA IN PATIENTS WITH CIRRHOSIS OF THE LIVER GIVEN CERTAIN NITROGENOUS SUBSTANCES*

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ONE of the serious complications of severe liver disease is the development of a comatose state that is frequently irreversible. Although hepatic coma is well recognized clinically, its onset has been difficult to predict, since no distinctive alterations in laboratory tests have been described.[1] The diagnosis of impending hepatic coma has been clarified, however, by the clinical observations of Adams and Foley,[2] who described mental disturbances and a characteristic tremor before the onset of the comatose state. In addition, a characteristic electroencephalographic pattern often occurs.[3]

A syndrome indistinguishable from impending hepatic coma has recently been described in patients with cirrhosis of the liver given certain ammonium-containing cation-exchange resins.[4] The cause of this reaction was not apparent. Elevated blood ammonia levels [5-8] and an intolerance to certain nitrogenous substances in patients with cirrhosis of the liver [7, 9, 10] suggested that this reaction was related to the ammonium contained in the resin.

The marked similarities between the resin reaction and spontaneously occurring hepatic coma prompted the present investigation, which demonstrates that apparently identical untoward effects can be provoked in patients with cirrhosis of the liver by the administration of ammonium chloride, di-ammonium citrate, urea or dietary protein.

TABLE 1. *Clinical and Laboratory Data.*

PATIENT	AGE	SEX	PERIOD OF STUDY	BODY WEIGHT	ASCITES	EDEMA	SERUM BILIRUBIN		THYMOL		BROMSULFALEIN RETENTION	URINARY UROBILINOGEN
					0-++++	0-++++	AFTER 1 MIN.	TOTAL	TURBIDITY	FLOCCULATION		
	yr.			kg.			mg./100 cc.	mg./100 cc.	cc.	0-++++	%	
R. P.	50	M	Initial	70.0	++++	++	1.4	3.2	5.5	+++	48	1:256
			Final	64.9	++++	+++	0.87	2.2	2.9	+	54	1:128
M. H.	65	F	Initial	59.4	+++	+	1.8	4.9	3.3	0	..	1:64
			Final	62.0	+++	++	0.52	1.2	2.6	+	46	1:32
A. S.	58	M	Initial	56.7	0	0	2.1	4.4	2.3	+	28	1:128
			Final	61.9	0	0	0.39	1.0	3.3	+++	27	...
A. C.	37	M	Initial	74.5	0	++	1.0	3.3	3.6	++++	32	...
			Final	79.5	0	0	0.84	2.8	3.4	++++	31	...
J. M.	61	M	Initial	99.3	+++	++	0.75	2.2	3.1	++	52	1:64
			Final	96.9	+++	++	0.31	2.0	2.6	+	..	...
I. B.	54	M	Initial	84.3	+++	+++	2.0	4.7	5.3	+++	48	1:128
			Final	69.7	0	+	0.40	1.7	4.5	+++	38	1:32
L. F.	40	M	Initial	69.3	+	0	1.4	3.0	4.7	+++	22	...
			Final	69.5	0	0	0.24	0.76	2.5	0	14	1:64
H. M.	59	M	Initial	107.7	±	±	1.1	2.7	1.1	0	36	1:64
			Final	108.5	0	±	0.37	1.1	1.1	0	..	1:32
J. P.	60	M	Initial	74.8	+	+	0.30	0.79	2.1	0	27	1:32
			Final	75.8	+	+	0.27	0.96	2.0	+	17	1:32

*Barium sulfate suspension (normal value <1.7 cc.).

MATERIALS AND METHODS

Nine chronic alcoholics with advanced cirrhosis of the liver diagnosed by history, physical examination and laboratory tests (Table 1) were studied on the Thorndike Metabolic Ward of the Boston City Hospital. The patients were ambulatory throughout the studies. No evidence of infectious disease or of gastrointestinal bleeding was observed. No medications other than those described below were administered. Four patients (R.P., M.H., I.B. and J. M.) with evidence of fluid retention were maintained on a constant low-sodium (about 10 milliequiv. per day) diet furnishing 75 gm. of protein and approximately 3000 calories per day. Four other patients were given diets with moderate or no salt restriction providing daily about 3000 calories and protein in quantities of 100 gm. (A. C.), 75 gm. (H. M., J. P.) and 50 gm. (L. F.). Patient A. S. re-

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ceived a regular hospital diet providing daily approximately 80 to 100 gm. of protein, 2000 to 2200 calories and unrestricted amounts of salt, except during a period of high-protein administration.

Four oral medications were employed. Ammonium potassium cation-exchange resin* was given in aqueous suspension. Ammonium chloride, *U. S. P.*, was administered as 0.3-gm. nonenteric-coated tablets and di-ammonium citrate, chemically pure, as 1-gm. capsules. The urea was dissolved in water or fruit juices. The 50 per cent solution of urea, *U.S.P.*, used in the first course of administration had an ammonia nitrogen content by analysis of approximately 0.029 gm. per liter; urea chemically pure, was used in the second course. Medications were given in three to five divided doses between 7 a.m. and 9 p.m. daily.

The untoward reaction that occurred during the administration of the substances used was similar in all the patients in whom it developed. Characteristically, it consisted of mental disturbances, a "flapping tremor" and electroencephalographic changes. Similar signs were not known to have occurred in any of the patients, except for J. M., prior to the administration of these substances.

The changed mental status was usually the first abnormal sign noted and frequently was recognized as an empty stare together with a lack of personal tidiness. It was difficult to reach the patient in conversation, and remarks often had to be repeated. As consciousness became more clouded, some patients manifested confusion and grossly inappropriate behavior. They performed acts very clumsily and had difficulty following directions, but usually claimed a feeling of well-being. None of the patients became comatose, although 1 (A. S.) exhibited a peculiar state of disturbed consciousness with automatism.

Occurring in close conjunction with the mental abnormalities was a characteristic tremor, which was absent at rest and developed on active maintenance of posture. This was most satisfactorily demonstrated if the patient held his arms forward with

TABLE 2. *Effect of Nitrogenous Substances on Clinical Signs and Laboratory Tests.*

PATIENT	MEDICATION					LABORATORY DATA*			
	TYPE	DATES GIVEN	DAILY DOSE	DURATION	TOTAL DOSE	DATE OF SAMPLE	SERUM pH_{38}*	CARBON DIOXIDE CONTENT	SERUM SODIUM
			gm.	*days*	*gm.*			*millimols / liter*	*milliequiv. / liter*
R. P.	NH_4-K Resin	5/9/51–5/12/51	30–60	4	210	5/9/51–5/12/51	...	25.9	125.0
							...	...	130.9
	NH_4-K Resin	5/16/51–5/18/51	30–60	3	150	5/16/51–5/18/51	...	...	132.5
							...	23.3	125.0
	NH_4Cl	8/6/51–8/9/51	3.3–13.2	4	31.5	8/6/51–8/9/51	...	23.3‡	125.0
							...	8.1‡	121.8
M. H.	NH_4-K Resin	7/17/51–7/25/51	30–60	9	375	7/17/51–7/25/51†	...	...	140.8
							...	13.5‡	139.5
	NH_4Cl	9/12/51–10/3/51	4.8–14.4	22	169	9/12/51–10/3/51†	7.42	26.1	143.6
							7.32	15.0	143.9
	$CaCl_2$	10/17/51–11/7/51	7–21	22	246	10/17/51–11/7/51†	7.48	27.2	136.0
							7.30	19.3	139.8
A. S.	Di-NH_4 citrate	10/24/51–11/6/51	10–20	14	214	10/24/51–11/6/51†	7.45	25.9	136.2
							7.38	19.1	138.3
	Urea	11/16/51–11/17/51	100	2	200	11/15/51–11/18/51†	...	24.9	139.4
							...	...	140.6
	Urea	11/26/51–11/27/51	100	2	200	11/26/51–11/28/51	7.45	23.7	138.9
							7.50	21.3	142.0
	Protein	12/29/51–1/18/52	150–200	21	3850	12/28/51–1/18/52	7.45	25.3	139.4
							...	...	138.2
A. C.	Protein	10/27/48–11/1/48	150	6	900	10/27/48–11/2/48	...	...	...
							...	...	...
J. M.	Protein	10/27/51–11/1/51	150	5	750	10/26/51–11/1/51	7.48	26.0	134.1
							7.48	25.0	135.6
I. B.	Di-NH_4 citrate	10/26/51–11/16/51	10–30	22	433	10/26/51–11/9/51§	7.45	26.8	134.0
							7.45	25.7	136.1
	NH_4Cl	11/24/51–12/7/51	9.9–15	14	169	11/23/51–12/8/51	7.44	21.5	139.5
							7.41	20.1	141.2
L. F.	Protein	12/18/51–1/1/52	100–150	15	2150	12/19/51–1/2/52	7.45	27.8	142.5
							7.45	26.2	143.1
	Urea	1/7/52–1/12/52	60–100	6	560	1/7/52–1/11/52	7.42	26.7	142.5
							7.40	29.6	143.8
H. M.	Protein	1/9/52–1/19/52	150	11	1650	1/8/52–1/18/52	7.40	27.1	143.2
							7.38	24.9	143 2
	Urea	1/23/52–1/27/52	100	5	500	1/23/52–1/29/52	7.38	27.5	143.2
							...	...	...
J. P.	Protein	10/30/51–11/12/51	150	14	2100	10/30/51–11/12/51	7.40	27.6	138.3
							7.45	27.0	141.8

*Laboratory and clinical data evaluated simultaneously.
†Blood specimen on this date obtained in afternoon.
‡Carbon dioxide combining power.
§Data obtained after period of maximum daily dose.

*This resin (Resodec) was supplied by Smith, Kline and French Laboratories, of Philadelphia; 1 gm. contains about 2.9 milliequiv. of ammonium.

hands and fingers extended. In this way, the tremor was seen as an irregular, coarse, flexion-extension movement at the metacarpophalangeal and wrist joints, sometimes more marked on one side, which when more severe involved the elbows and shoulders. Hereafter, it is referred to as the flapping tremor.

The electroencephalographic changes* that developed in some of the patients were similar to those described by Foley, Watson and Adams[3] in patients developing hepatic coma. Typically, there are bilaterally synchronous slow waves of two-per-second frequency that in the early stages occur in bursts, usually separated by cortical alpha rhythm. The bursts appear at first in the frontal regions but later increase in duration and spread laterally and posteriorly until the entire record is of slow activity. These abnormal patterns were seen in the patients in this study only during a clinical reaction.

As soon as the clinical reaction became evident, the substance being administered was withdrawn. The mental disturbances, tremor and electroencephalographic changes reversed within a day or two. No residua were noted.

Laboratory tests performed to estimate hepatic function included bromsulfalein retention forty-five minutes after the intravenous injection of the dye (5 mg. per kilogram of body weight), "one-minute" and "total" serum bilirubin,[11] thymol turbidity and flocculation[12] and urinary urobilinogen.[13] Serum $pH_{38}°$ was determined with the bi-color standards of Hastings and Sendroy,[14] serum carbon dioxide content or combining power by the method of Van Slyke and Neill,[15] and serum sodium and potassium concentrations by internal standard flame photometry.[16] Blood ammonia* levels were measured by a modification of the micro-distillation technic of Conway.[17] Twenty-six determinations on thirteen normal subjects (8 male and 5 female) revealed a mean value of 2.04 with a standard deviation of 0.45

TABLE 2. (*Concluded.*)

PATIENT	LABORATORY DATA* (*Continued*) SERUM POTASSIUM	BLOOD AMMONIA	BLOOD NONPROTEIN NITROGEN	TREMOR	CLINICAL DATA* MENTAL	DATE	ELECTROENCEPHALOGRAM COMMENT
	milliequiv./liter	*gamma of nitrogen/cc.*	*mg./100 cc.*				
	4.2	...	...	None	None	.....	.....
	4.0	...	...	Marked	Moderate	.....	.....
R. P.	4.2	...	...	None	None	5/16/51	Slight abnormality — not characteristic
	...	...	...	Marked	Moderate	5/18/51	Bursts of slow activity
	4.1	...	...	None	None	5/22/51	?Slight abnormality
	3.9	...	...	Marked	Moderate	8/9/51	Frequent bursts of slow activity
	3.6	...	...	None	None	.....	.....
	3.2	...	...	Marked	Marked	.....	.....
M. H.	3.2	3.7	...	None	None	9/17/51	Normal
	2.9	15.0	24.4	Marked	Moderate	10/3/51	Bursts of slow activity
	2.9	3.6	...	None	None	10/4/51	Slight abnormality
	3.0	3.2	...	None	None	11/7/51	Normal
	3.4	3.2	...	None	None	10/22/51	Normal
	3.5	6.1	28.0	Moderate	Moderate	11/6/51	Slight abnormality
	3.6	2.8	...	None	None	11/9/51	Normal
	3.9	...	29.5	Marked	Marked	.....	.....
A. S.	4.0	3.4	23.3	None	None	11/27/51	Normal
	4.0	3.2	49.6	Marked	Marked	11/28/51	Frequent bursts of slow activity
	4.0	2.2	26.0	None	None	11/29/51	Slight abnormality — rare slow activity
	4.1	2.7	36.4	None	None	.....	.....
A. C.	...	...	...	None	None	.....	.....
	...	...	...	Moderate	Marked	.....	.....
J. M.	3.4	3.8	...	None	None	10/26/51	Normal
	3.7	4.4	...	Moderate	Moderate	11/1/51	Slight abnormality
	4.0	2.6	...	None	None	10/24/51	Normal
	3.8	3.0	...	None	None	.....	.....
I. B.	3.9	3.2	...	None	None	.....	.....
	3.9	3.7	...	None	None	.....	.....
	4.1	2.1	...	None	None	12/17/51	Normal
L. F.	4.3	2.8	28.0	None	None	.....	.....
	4.2	1.8	22.5	None	None	.....	.....
	4.2	2.9	62.0	None	None	.....	.....
	4.3	2.2	...	None	None	1/18/52	Normal
	4.3	2.6	34.0	None	None	.....	.....
H. M.	4.4	2.6	32.0	None	None	.....	.....
	...	...	...	None	None	.....	.....
J. P.	3.7	2.8	...	None	None	.....	.....
	4.0	3.2	...	None	None	.....	.....

*We are indebted to Dr. Joseph Foley, of the Department of Neurology, Boston City Hospital, for his interpretation of the records.

*The values are those obtained with 1 cc. of whole blood taken into 100 per cent carbon dioxide and potassium oxalate. Ammonia was permitted to diffuse for sixty minutes. No corrections were made for the differences in the diffusion rates of ammonia between ammonium sulfate standard and blood or for the deaminating action of the alkali. The data thus obtained represent nitrogenous substances present in blood capable of forming ammonia as well as any free ammonia. All values are given in terms of blood ammonia nitrogen and hereafter are referred to as blood ammonia.

gammas of ammonia nitrogen per cubic centimeter of blood. Blood sugar and nonprotein nitrogen concentrations were determined by the methods of Folin and Wu.[18] Urine ammonia concentration was obtained by permutit extraction as described by Folin.[18]

All blood specimens were drawn from an antecubital vein with minimal stasis at approximately three or four hours after breakfast and before the daily medication was given, unless otherwise specified.

Results

The reaction resembling impending hepatic coma occurred in 5 of the 9 patients studied. In 2 patients (R. P. and M. H.), who had this reaction to an ammonium-containing resin, similar difficulties with orally administered ammonium chloride developed. A third patient (A. S.) manifested the reaction with one course of di-ammonium citrate and three courses of urea, respectively, but not with a high dietary intake of protein. The reaction was also seen in 2 additional patients (A. C. and J. M.) when the protein content of the diet was increased. Four other patients, however, failed to show any untoward effects when given a course of ammonium chloride (I. B.), di-ammonium citrate (I. B.), urea (L. F. and H. M.) or increased dietary protein (L. F., H. M., J. P.).

The sequence of events in those patients who developed the reaction is considered in some detail. The results of the laboratory determinations are summarized in Table 2.

Patient R. P. was given 60 gm. of an ammonium potassium cation-exchange resin per day after having been in the hospital for four weeks. On the fourth day of therapy, mental disturbances and a flapping tremor developed, and the resin was stopped after 30 gm. had been given that day. On the following morning, these abnormalities were no longer present. He remained mentally clear and without tremor for the subsequent three days, after which a second course of the same resin was started at the same dosage. On the second day of this course, mental disturbances again appeared and by the third day were marked and associated with a prominent flapping tremor. Resin administration was discontinued after he had received 30 gm. on the third day. An electroencephalogram at this time showed typical bursts of slow activity, which had not appeared on a tracing taken two days previously. Within twenty-four hours after the resin had been stopped, the abnormal clinical signs disappeared. About three months later, the patient was rehospitalized and given ammonium chloride orally for four successive days in doses of 5.1, 9.9, 13.2, and 3.3 gm. per day, respectively. These doses were calculated to provide a quantity of ammonium comparable to that contained in the resin administered previously. The untoward reaction occurred on the fourth day and consisted of considerable mental change, a marked flapping tremor and frequent bursts of high-amplitude, slow waves in all leads of the electroencephalogram. By the following day, he was much improved both clinically and by electroencephalogram, and two days after the ammonium chloride had been stopped, he appeared as on admission, showing no mental disturbance or flapping tremor.

During the two courses of resin and one course of ammonium chloride administration, no significant change in serum potassium concentration or consistent change in serum sodium concentration occurred. In addition, serial electrocardiograms taken during the two courses of resin therapy revealed no significant changes. During the course of ammonium chloride administration, however, the carbon dioxide combining power decreased considerably, suggesting an acidosis.

Patient M. H. was given an ammonium potassium cation-exchange resin after having been in the hospital for two months. She received 30 gm. a day for three days, 45 gm. a day for three days, 60 gm. a day for two days and 30 gm. on the final day of therapy, when she exhibited marked confusion and a flapping tremor. One day after cessation of the resin, the tremor was gone and the mental disturbances had essentially disappeared. Serial determinations revealed no significant change in serum sodium and slight, if any, diminution in serum potassium from the control period to the time of reaction. The carbon dioxide concentration at the time of the reaction was 13.5 millimols per liter. About a month and a half later, ammonium chloride was administered in doses calculated to contribute a quantity of ammonium similar to that contained in the resin given previously. She received 4.8 gm. a day for eleven days, 9.6 gm. a day for seven days, 14.4 gm. a day for three days, and 6.0 gm. on the last day of administration, when the ammonium chloride was stopped because of the onset of mental disturbances and a flapping tremor. Within one day of cessation of the medication, these abnormal signs had disappeared. The electroencephalogram (Fig. 1), which was normal prior to the institution of ammonium chloride, showed at the time of the clinical reaction typical bursts of slow activity, predominantly in the frontal and parietal fields. These were no longer present on an electroencephalogram taken twenty hours later. During the three-week course of ammonium chloride, the blood ammonia concentration gradually rose from a control value of 3.7 to 6.6 gamma per cubic centimeter on the morning of the day of reaction. The blood ammonia concentration measured at the peak of the reaction, which occurred in the afternoon and after 6.0 gm. of ammonium chloride had been given that day, was found to be 15 gamma per cubic centimeter. Serum sodium and potassium levels measured at this time showed no significant change from control values, but the

serum carbon dioxide content and pH had dropped respectively to 15.0 millimols per liter and 7.32 from control values of 26.1 millimols per liter and 7.42.

In an effort to determine the role of acidosis in the development of the reaction, this patient was given calcium chloride orally beginning two weeks later at a dosage comparable in chloride content to the previously administered ammonium chloride. She received 7 gm. a day for eleven days, 14 gm. a day for seven days, 21 gm. a day for three days and 12 gm. on the final day of administration. Her only complaints at the termination of the course of calcium chloride administration were mild generalized abdominal distress and anorexia, and she displayed neither mental aberration nor tremor. An electroencephalogram at this time was normal. A blood specimen drawn on the afternoon of the final day of the calcium chloride regimen, after 12 gm. had been given that day, showed a decrease in serum carbon dioxide content and pH to 19.3 millimols per liter and 7.30, respectively, whereas no significant change in serum sodium or potassium concentration occurred. At this time, the blood ammonia concentration was 3.2 gamma per cubic centimeter as compared to a control value of 3.6 gamma, and the urinary ammonia nitrogen content had risen from an average daily excretion of approximately 0.2 gm. during the control period to 1.6 gm. on the last day of calcium chloride administration.

Patient A. S., after a control period of a week, was given di-ammonium citrate according to the following dosage schedule: 10 gm. a day for five days, 20 gm. a day for eight days and 4 gm. on the fourteenth or final day. Every evening during the last five days of administration mental changes and the characteristic tremor, becoming more prominent on each successive evening, developed. During the day, however, he showed no such abnormalities until the thirteenth day, when they were slight but definite; on the fourteenth day, they were quite marked, and the medication was stopped. Since the di-ammonium citrate was given only during the day, it was believed that the disturbances that occurred at night were related to the dosage schedule. Within two days of cessation of the medication, the abnormal signs were gone. An electroencephalogram taken just after the height of the reaction was technically poor but showed abnormalities suggestive of the characteristic pattern, whereas the control record and another taken three days after the reaction were normal. The blood ammonia level, which had been as high as 4.7 gamma per cubic centimeter during the week prior to the institution of the di-ammonium citrate, decreased gradually to 2.2 gamma per cubic centimeter after the first nine days of the medication and then rose to 4.1 gamma at the height of the reaction on the morning of the final day of administration. In the afternoon, however, when the abnormal signs were improving and the electroencephalogram described above showed only slight changes, the blood ammonia level was 6.1 gamma per cubic centimeter. Serum sodium and potassium concentrations measured at this time showed no significant change from control levels, and the serum carbon dioxide content and pH decreased moderately. The blood nonprotein nitrogen level was 28.0 mg. per 100 cc.

Ten days later, the patient was given urea in a dosage of 100 gm. per day. On the evening of the second day, he became confused, and the urea was discontinued. On the following day, mental disturbances and a flapping tremor were marked, and a blood specimen was drawn in the afternoon for serum sodium and potassium and blood nonprotein nitrogen concentrations, which showed no significant change from previous values. The clinical abnormalities noted did not disappear until forty-eight hours after the medication had been stopped. Nine days after the first course of urea, a second course was instituted at the same dosage. On the evening of the second day, mental changes and a flapping

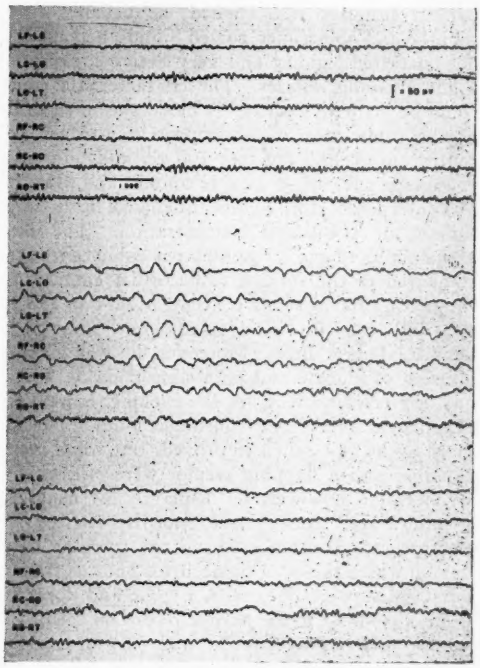

FIGURE 1. *Electroencephalographic Tracings on Patient M. H. The upper tracing (taken on September 17, 1951) is a control and shows no abnormality. The middle tracing, taken at the peak of clinical reaction to ammonium chloride (October 3, 1951), shows typical slow activity. The lower tracing, which was taken twenty hours later and twenty-four hours after cessation of ammonium chloride administration, no longer shows the characteristic waves. (LF, left frontal; LC, left central; LO, left occipital; LT, left temporal; RF, right frontal and so forth.)*

tremor were obvious, and the urea was discontinued. Although he was quite active during that evening, he manifested a bizarre state of disturbed consciousness early on the following morning. His eyes were wide open and he appeared alert as he lay on his bed with his hands behind his head, but he did not respond to spoken voice or flinch when the observer's hand was directed rapidly toward his eyes. Whenever his hands were removed from behind his head, he invariably returned them to the same position in an automatic fashion. When a painful stimulus was applied, he usually winced slightly and sometimes cursed simultaneously. He demonstrated rigidity and very active sucking and slight grasping reflexes. The characteristic tremor could be made out easily. A blood specimen drawn at this time revealed a nonprotein nitrogen concentration of 49.6 mg. per 100 cc. and only small changes in the carbon dioxide content and pH of the serum. There was no significant change in the serum sodium or potassium concentration. The blood ammonia level was 3.2 gamma per cubic centimeter, compared to the control value of 3.4 gamma, and the fasting blood sugar concentration was 153 mg. per 100 cc. An electrocardiogram showed no definite abnormalities. Moreover, he was given an infusion of glucose and potassium chloride without any appreciable effect. In the evening, however, he began to converse and consumed fluids. The next morning he was much improved, but some mental clouding and a flapping tremor were still evident. By evening, however, he displayed his usual personality, and tremor could not be elicited. An electroencephalogram done on the morning of the day on which the reaction occurred showed frequent bursts of slow activity with a spike and dome pattern, in contrast to the normal record on the day before; a much improved record with only an occasional burst of abnormal waves was taken on the following day.

Beginning about a month later, after a two-week period of a dietary protein intake of 75 gm. per day, the patient was provided with 150 gm. of dietary protein daily for a week and 200 gm. daily for two weeks. No abnormal signs developed. Laboratory tests revealed a rise in blood nonprotein nitrogen concentration and a questionable increase in the blood ammonia level, but there was no significant change in serum sodium and potassium concentrations. To determine whether the patient was still capable of developing the characteristic untoward reaction, the dietary protein was reduced to 75 gm. per day, and two days later he was started on urea by mouth. He received 80 gm. on tne first day and only 40 gm. on the second, when urea administration was discontinued because of clouding of consciousness and a slight but definite flapping tremor. Within a day, these abnormal signs had disappeared.

Patient A. C., after a seven-week period of a diet containing 100 gm. of protein daily, was given a diet providing 150 gm. of dietary protein a day. After five days of this increased protein intake, he became anorexic, and after six days, he exhibited marked confusion and a flapping tremor. The protein intake was reduced, and within two days he was mentally clear and showed no tremor. Electrolyte studies were not carried out in this case.

In patient J. M. moderate flapping tremor with mental sluggishness spontaneously developed a week before hospital admission. At that time the blood ammonia concentration was 10 gamma per cubic centimeter, and the serum concentrations of sodium and potassium were 129.2 and 3.4 milliequiv. per liter, and the serum carbon dioxide content was 26.3 millimols per liter. An electroencephalogram disclosed typical bursts of large slow waves in all leads. One day after entry, the flapping tremor was barely evident, the sensorium was clearer, and an electroencephalogram showed less abnormality than on the previous tracing. Laboratory tests revealed a blood ammonia level of 5.6 gamma per cubic centimeter, serum sodium and potassium concentrations of 134.8 and 3.1 milliequiv. per liter, and a serum carbon dioxide content of 23.8 millimols per liter. He was provided with a constant diet containing 75 gm. of protein a day. A week later, the blood ammonia concentration was 3.8 gamma per cubic centimeter, and he showed no clinical or electroencephalographic abnormalities. There were no significant changes in the serum electrolyte concentrations (see control values in Table 2). At this time, the protein content of the diet was increased to 150 gm. a day. After three days of this diet, the flapping tremor was again apparent, and after five days, mental changes occurred in addition, and he refused all his meals; an electroencephalogram was abnormal but did not show the characteristic waves. The blood ammonia level was 4.4 gamma per cubic centimeter, and there were no significant changes in the serum sodium and potassium concentrations or pH. On the following morning he was clinically improved, and a blood ammonia level was 3.8 gamma per cubic centimeter without significant change in the serum pH or concentrations of the electrolytes measured. The 75-gm. protein diet was then reinstituted. During the ensuing week, he showed no mental disturbances or flapping tremor, and a blood ammonia level, one week after the protein intake had been reduced, was 4.6 gamma per cubic centimeter with no significant change in the serum pH or concentrations of sodium and potassium. An electroencephalogram showed less abnormality than the previous one.

Four additional patients with advanced liver disease given nitrogenous substances manifested no abnormal clinical signs or consistent changes in blood chemical values except, perhaps, for a rise in the blood ammonia concentration. One patient (I. B.) received a course of di-ammonium citrate and ammonium chloride, 2 (L. F. and H. M.) a

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course of increased dietary protein and of urea, respectively, and a fourth (J. P.) a course of increased dietary protein. Patient H. M. had had the characteristic untoward response to an ammonium-containing resin two years previously, and L. F. had recovered from a spontaneous episode of impending hepatic coma, characterized by mental disturbances and a flapping tremor, about three weeks prior to beginning the course of increased dietary protein.

Discussion

A syndrome indistinguishable from impending hepatic coma and typically consisting of mental disturbances and a characteristic tremor and electroencephalographic pattern was produced in patients with advanced cirrhosis by the administration of certain nitrogenous substances. An apparently identical syndrome has been reported in patients with cirrhosis given cation-exchange resins containing ammonium.[4] Untoward reactions to certain of these substances have been noted previously in patients with cirrhosis. Van Caulaert and his coworkers[9] described marked mental disturbances in 3 patients with Laënnec's cirrhosis after the oral administration of 10 gm. of ammonium chloride to 2 and 18 gm. of urea to 1. One of these patients, in addition, exhibited uncontrollable clonic jerking of the limbs. Kirk[7] observed a semicomatose state in 3 of 28 patients with cirrhosis given 10 gm. of ammonium citrate by mouth. Transient mental disturbance occurring in patients with cirrhosis after oral urea administration were also reported by Gaustad.[10] Another of his patients developed transient coma after consuming 250 gm. of dried milk a day.

The mechanism of the reaction observed in the present study is not clear. Several possible explanations, nevertheless, may be considered. The fact that three of the substances administered contained ammonium (resin, ammonium chloride, and di-ammonium citrate) suggests that the ammonium either directly or indirectly gave rise to the reaction. The urea and protein administered may have been transformed into ammonium by the action of intestinal bacteria, which may explain the delayed untoward effect of urea as compared with di-ammonium citrate in 1 patient (A. S.). The importance of the liver in ammonium metabolism lends support to this hypothesis. Extirpation of the liver in dogs results in a marked increase in the blood ammonia concentration.[19] Eck-fistula dogs fed large quantities of protein, moreover, frequently exhibit a comatose state, which has been shown to be associated with an increased blood ammonia concentration.[20] Elevated blood ammonia levels,[5-8] especially in the presence of coma,[8] and decreased tolerance by blood ammonia measurements to orally administered ammonium salts[5-7, 21, 22] have been reported in patients with cirrhosis. The disturbed ammonium metabolism of such patients may be related to a decreased ability of the liver to handle ammonia, to a partial exclusion of the liver from the portal circulation by the portosystemic anastomoses, or to both.

If ammonium were directly responsible for the reaction observed, a relation between the abnormal clinical signs and the blood ammonia level might be expected. Van Caulaert et al.[9] attributed the clinical abnormalities following ammonium chloride administration to high blood ammonia concentrations. Kirk,[7] however, observed higher blood ammonia levels than Van Caulaert in patients without mental disturbances. In the present study, the correlation between the blood ammonia concentrations and the abnormal signs observed was not consistent enough to establish a relation. This lack of correlation may have been due to the nonspecific nature of the method used, since there is no accurate knowledge of the sources of the ammonia liberated from the blood during the analytical procedure. An alternate possibility is that the reaction was dependent on the tissue rather than on the blood concentration of ammonia.

The inciting substances also may have produced the untoward reaction by forming or causing formation of a toxic substance other than ammonium, such as an amine. No evidence was obtained from the present study, however, to elucidate this possibility.

Alterations in serum pH and sodium, potassium and carbon dioxide concentrations and in blood nonprotein nitrogen levels were also considered as possible causes of the abnormal signs, but serial measurements failed to reveal any changes correlating with the reactions observed. The fasting blood sugar concentration was measured once during a severe reaction (A. S.) and found to be 153 mg. per 100 cc. One patient (M. H.), who was acidotic during the reaction to ammonium chloride, did not show the characteristic abnormal signs when made acidotic to a similar degree with calcium chloride. Nevertheless, it is conceivable that intracellular electrolyte changes not reflected to a measurable extent in the serum were responsible.

Since in the present study the nitrogenous substances were administered only to subjects with liver disease, it is not known whether hepatic damage is requisite for the development of this reaction. If this reaction is not specific for patients with cirrhosis, they appear unusually more susceptible to it when given these substances widely employed in therapeutics. The reason for the individual variation in susceptibility was not apparent, but was not related to liver function as measured by the tests employed.

The untoward reaction was reversible in every case studied, and there were no apparent clinical residua. Furthermore, there was no evidence that any of the substances used augmented the liver disease. The marked resemblance between this reaction and impending hepatic coma, however, implies that the administration of these substances to patients with cirrhosis may be hazardous.

Summary and Conclusions

The effects of an ammonium potassium cation-exchange resin, ammonium chloride, di-ammonium citrate, urea and increases of dietary protein were observed in 9 chronic alcoholics with advanced cirrhosis.

Each of the substances was capable of provoking a reaction clinically indistinguishable from impending hepatic coma and characterized by mental disturbances, a flapping tremor and often distinctive electroencephalographic changes.

Four of the patients, however, showed no untoward effects when one or more of these substances were administered in separate courses.

Biochemical measurements performed before, during and after these reactions revealed no consistent changes. The blood ammonia concentration seemed to correlate best with the reactions observed, but the correlation was not dependable enough to substantiate a relation.

One patient made acidotic with calcium chloride to a similar degree as during her reaction to ammonium chloride did not show the characteristic reaction.

The administration of these nitrogenous substances to patients with liver disease may be hazardous.

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UTILIZATION OF CHOLANGIOGRAM DURING EXPLORATION FOR BILIARY ATRESIA*

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THE results of surgical exploration of infants with biliary atresia have been discouraging, for only a small percentage of these patients have proved to have a mechanical block that could be relieved surgically. This experience prompted an evaluation of the surgeon's approach to the problem.

Cases of obstructive jaundice appearing in the neonatal period, which persisted with increasing intensity beyond five weeks, were diagnosed as congenital atresia of the bile ducts. Although the jaundice might be imperceptible during the first few days of life, in four or five weeks the syndrome of obstructive jaundice developed with deep icterus, mahogany-colored urine and clay-colored stools. The baby usually developed normally. Some babies because of the inability to retain or to assimilate their formulas failed to gain weight at a normal rate. At six to eight weeks of life the liver was enlarged, the edge extending 4 or 5 cm. below the costal margin, with occasional splenomegaly. On laboratory examination, the total serum bilirubin rose from 20 to 30 mg. per 100 cc., with 60 to 90 per cent showing the direct van den Bergh response. The serum alkaline phosphatase became elevated above 15 Bodansky units. The urine and fecal urobilinogen excretion was within normal limits. Later in the course of the disease when severe jaundice developed, evidence of hepatitis was present — that is, cephalin-cholesterol flocculation was ++++, and thymol turbidity, 2 to 4 units. Serum cholesterol esters were reduced below 75 per cent of total cholesterol. The clotting mechanism was impaired, with a prolonged prothrombin time. The total serum protein and albumin-globulin ratio were usually normal.

When the baby was four to eight weeks of age surgical exploration was usually performed in the hope of finding and correcting an atresia of the extrahepatic system. At laparotomy, the liver was enlarged but of normal consistence, unless the jaundice had existed for several years and chronic hepatitis with "hobnail" liver had developed. The gall bladder was small and usually contained white, viscid material with a slightly yellow tinge.

The surgeon explored the regions of the common bile duct, hepatic duct and porta hepatis with the hope of finding a dilated duct system proximal to an atresia. This was a difficult surgical dissection, and in most cases no dilated hepatic or common duct was found. Instead, these structures were of small caliber and were assumed to be atretic. Yet some of these babies, despite a hopeless surgical prediction, completely lost their icterus and regained good health. These observations prompted a change in operative routine that simplified the surgical procedure and reduced the danger of injury to small structures, which, in the patients who made recoveries, were evidently capable of becoming dilated and functionally adequate. The first innovation in technic was to insert a needle into the gall bladder and inject methylene blue solution before any dissection was done. Blue dye in the duodenum proved patency of the cystic duct and common bile duct. The gastrohepatic ligament was then explored to rule out an atresia of the hepatic ducts. Again, a number of these patients recovered completely. Recently, we found that outlining the hepatic system with Diodrast and obtaining x-ray films taken with portable apparatus in the operating room simplified the procedure still further and eliminated the possibility of damage to a minute but patent duct system.

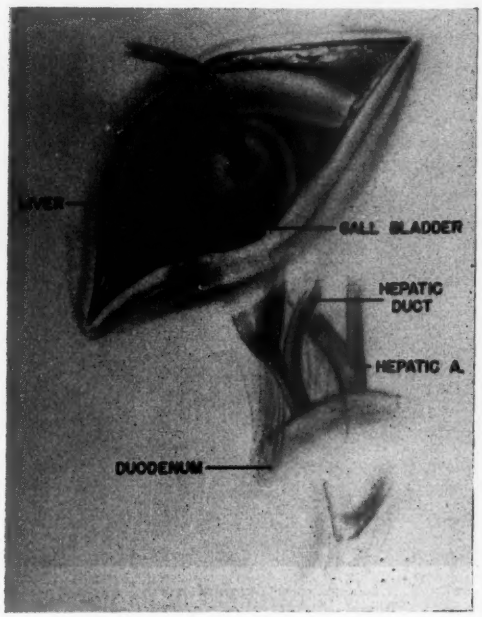

FIGURE 1. *Polyethylene Catheter Tied in the Fundus of the Gall Bladder with a Purse-String Suture.*

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The following technic for on-the-table cholangiograms was used. The operating table was prepared by placing a cassette carrier loaded with a cassette beneath a thin blanket, and the patient was positioned over this. The gall bladder and liver were exposed through a short right subcostal incision. A biopsy of the liver was taken, and any gross abnormalities of the biliary system noted. A polyethylene catheter was inserted into the fundus of the gall bladder and tied in place with a purse-string suture (Fig. 1). The biliary system was flushed with warm saline solution to wash out particles of inspissated bile and to relax the sphincter of Oddi. The patient was rotated to a right oblique position to remove the lumbar spine from the desired roentgenographic field. A portable x-ray unit was brought into position over the patient. Ten cubic centimeters of warm 35 per cent Diodrast was instilled into the gall bladder, and the film was exposed as the last cubic centimeter was injected. If a patent biliary tree was demonstrated, no further surgery was indicated. If an anomaly of the duct system was visualized by x-ray study, surgical exploration with an attempt to relieve the obstruction was indicated.

FIGURE 2. *Cholangiogram Obtained during Exploration for Biliary Atresia in a Newborn Infant.*
The photograph has been retouched to show the biliary tree clearly.

DISCUSSION

Four cases of neonatal obstructive jaundice have been investigated in this manner. In 3, a patent biliary system was demonstrated by x-ray examination (Fig. 2). In 1 case no duct system was found. This, in addition to our previous experience, made us doubt the diagnosis of atresia of the extrahepatic biliary ducts in some patients. Exploration with instillation of blue dye originally, and later radiopaque dye, led us to the conclusion that small patent ducts were present in some cases. Patterson[1] postulated that these patients belonged in the group with mucoviscidosis. Ladd[2] repeatedly stressed the fact that not infrequently the obstruction was due to inspissated bile. The jaundice was thought to be due to thick, tenacious biliary secretions inspissated in the bile ducts, causing mechanical obstruction. On a recent patient, the viscosity of the fluid from duodenal drainage as measured in an Ostwald tube was seven minutes as compared with a normal reading of three minutes. On this premise these patients have been started on a medical regimen to decrease the viscosity of the biliary and pancreatic secretions. Patterson's regimen included: intravenously injected bile salt, sodium dehydrocholate, (Decholin Sodium, Ames Company, Incorporated), 2 to 5 cc. every other day for one week, and orally administered bile salts (Ketochol, G.D. Searle and Company.) 250 mg. every four hours during the first week and three times a day for as long as a month. The bile salts given by mouth occasionally caused nausea and vomiting after the biliary tree was functioning well. In other respects, the usual feeding schedule was followed.

SUMMARY

A method is presented by which patency of the biliary system in infants with increasing obstructive jaundice may be demonstrated by the instillation of radiopaque dye into the gall bladder. The advantages are twofold: the small surgical procedure involves a minimal risk to the patient, and there is no chance of traumatizing the small ducts with this diagnostic method. It is postulated that some of the cases, diagnosed as biliary atresia because of inability to demonstrate a patent extrahepatic biliary tree, fall into the group of mucoviscidosis.

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MEDICAL PROGRESS

THE IMPORTANCE OF COXSACKIE VIRUSES IN HUMAN DISEASE, PARTICULARLY HERPANGINA AND EPIDEMIC PLEURODYNIA*

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"VIRUS infection" is possibly the diagnosis most frequently made by physicians today. It is generally supposed that this term includes a large proportion of the unclassified minor infectious diseases. The agents that cause these so-called "minor diseases" appear to have a very special talent — namely, an ability to preserve the human subject for innumerable subsequent attacks of similar illnesses. Because they represent more subtle categories of human parasites, they do not attract attention by destroying their hosts as do the so-called "major" but more easily controlled disease agents. Thus in the biologic sense they are far more successful parasites than the more virulent ones, since by approaching symbiosis the production of disease has become quite unimportant in the maintenance of their parasitic cycle in man. Because they produce extremely mild or even inapparent infection far more often than they produce the more easily recognized and characteristic disease entities, the true pattern of their parasitic existence is not realized. Hence communicable-disease measures that are successful in controlling many of the better defined and much more clinically obvious serious infections at present fail when applied to infectious processes that are largely unrecognized and certainly poorly understood. The agents responsible for these "virus infections" are quite satisfied to disarm their human host by producing misery, discomfort and incalculable disability on a temporary and piecework basis.

In addition to the general and noncommittal term "virus infection" that is so fashionable today, terms frequently applied to this hodgepodge of illnesses are: "common cold," "minor respiratory infections," "la grippe," "influenza-like disease," "winter vomiting disease," "intestinal influenza" and even "nonparalytic poliomyelitis." The lack of accurate definitions and recognizable reference points in this large area of minor illnesses renders it likely that a direct research attack would be as futile as an attempt to overcome a grasshopper plague with a platoon of riflemen.

This is not to say that all is hopeless and that effective means for rational investigations of this kind of communicable-disease problem are not available. A most effective method based upon the old military principle of "divide and conquer" has been tried and has been proved to be effective. Although it was unconscious and certainly undefined, this principle of segregating elements of the enemy for special attention and intensive treatment was actually used in the solution of "pneumonia." Thus out of the conglomeration, "pneumonia," were segregated such distinct clinical entities as pneumococcal and other bacterial pneumonias, influenzal pneumonia, psittacosis and Q fever. Unexplained, etiologically, is a small residue known as atypical pneumonia. It is conceivable that "virus infections" will eventually be resolved in somewhat the same manner.

A major step in this direction has been the recent recognition of an entirely new group of human viruses known as Coxsackie viruses. Already lumped under this general and rather peculiar term are 15 immunologically distinct agents of human disease that were completely unknown three or four years ago. Similar in size and biologic properties to poliomyelitis virus, like that organism, they are extremely prevalent in children in the summertime. Unlike many human viruses (such as poliomyelitis viruses) the so-called Coxsackie viruses can be demonstrated with ease in a cheap and widely available laboratory animal — the suckling mouse. As a consequence of this ease of demonstration, an extensive literature relating to their properties and to their occurrence in man has accumulated within a span of four years.

There appears to be some confusion concerning the nature and properties of Coxsackie viruses. Some of this confusion undoubtedly stems from the tendency of many workers to lump large numbers of different strains of viruses representing 12 to 15 immunologically different types and two or more quite distinct groups under the simple and unqualified term "Coxsackie virus." Thus many statements applicable only to certain strains and types of viruses appear in the literature as comments on Coxsackie viruses in general.

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Properties of the Viruses

Coxsackie virus is an inclusive term that has been applied to at least two large groups of heterogeneous viruses of man. First described in 1948 by Dalldorf and Sickles,[1] who recovered the initial strains from 2 patients with a clinical diagnosis of paralytic poliomyelitis in Coxsackie, New York, these agents are grouped together chiefly because of their ability to produce characteristic lethal illnesses in suckling mice and hamsters.

The immunologic specificity of many of the available strains has been pointed out,[2-7] and it is now possible to use rather simple procedures[8] to characterize new strains according to serologic behavior. In addition, Dalldorf has indicated certain marked pathologic differences produced by these viruses in suckling mice and has proposed further segregation of them on this basis into Groups A and B.[9, 10]

Group A viruses, which include 8 to 11 serologically distinct types, characteristically produce extensive liquefaction necrosis of skeletal muscles and virtually no other observable pathologic findings in suckling mice and suckling hamsters. These species, after their first two or three weeks of life, cannot be infected by Group A viruses. Except for a few strains that produce muscle necrosis in chick embryos,[11, 12] Group A viruses are known to infect only the chimpanzee, which exhibits no more than an intestinal carrier state followed by an immune response.[7, 13, 14] One type has been grown in tissue culture,[12, 15] and cockroaches have been found to harbor Coxsackie viruses after experimental infection.[16]

The Group B viruses were originally so classified when Dalldorf found that they produced only mild to moderate focal muscle lesions while also causing a characteristic encephalopathy and panniculitis. Additional work by Pappenheimer[17-20] and others[21] showed that certain of the strains classified by Dalldorf in Group B produced extensive pancreatitis, as well as other visceral lesions, in both suckling mice and adult mice. Contrary to one report,[22] the use of cortisone is not essential in the serial propagation of the Connecticut 5 strain in adult mice.[18] These last findings, particularly those regarding adult mice, have been fully confirmed by us for other Group B viruses as well as for Connecticut 5 and appear to provide a sound basis for sharply segregating these viruses from those in Group A. As pointed out below, this separation of Coxsackie viruses into at least two distinct groups is further justified by controlled epidemiologic studies of their behavior in their only known natural host — man.

Table 1. *Current Knowledge of Some Attributes of Eight Immunologically Distinct Group A "Coxsackie Viruses."*

Virus Type	Illness in Man*	Suckling Mice				Adult Mice	
		Illness	Pathology			Illness	Pathology
			myositis	*central nervous system*	*viscera*		
Albany Type 2[2]	Repeatedly and significantly associated with herpangina[23-25] in controlled epidemiologic studies						
Albany Type 3[2]	85.6% of 99 cases infected with one of these viruses (except Type 3) from 1949 to 1951						
High point[26] (Albany Type 4)[2]		Generalized involvement of all skeletal muscle groups, resulting in flaccid paralysis followed by death	Generalized necrosis of all skeletal muscles except tongue[1, 10, 21, 28, 29]	None	None	None	None
H1[26]							
NIH 248[22]							
H2[26]							
(NIH 233)[22] (Partial antigenic relation to Albany Type 3)[7]							
H3[26]							
H4[26]							
Albany Type 1[2] (Easton 2)[23, 24] (B. J.)[25]	Unknown significance[23, 2, 24, 26]	Stiffness and paralysis of limbs, characteristic wrist drop, curvature of torso followed by death[7]	Patchy, not as extensive as other Group A types[7]	None	None	None	None

*Practically all strains have been recovered from cases of clinical poliomyelitis, but their relation, if any, to this disease is obscure.

†Asymptomatic infections; fecal and oropharyngeal carrier states; viremia noted in some experiments; development of type-specific neutralizing and complement-fixing antibodies.

Tables 1 and 2 review some of the reported attributes of 12 immunologically distinct types of Coxsackie viruses. The agents are listed according to Dalldorf's classification, a grouping that we have found quite useful as a working classification for the agents with which we have had some experience and that have been adequately characterized in the literature. Other strains are known to exist (we have several such examples) but their properties are not sufficiently well known at this time to warrant inclusion in these tables.

All the Coxsackie viruses appear to be extremely small, exhibiting a size range commonly accepted than 20 millimicrons. This apparent disagreement between the calculated results of different physical technics for estimating size has been observed repeatedly in studies of other viral agents and may be due to the fact that the ultrafiltration method measures only the smallest particles whereas the ultracentrifugation measures the average and possibly more numerous particles.

All the strains exhibit complete resistance to ether and also to such antibiotics as have been tested (penicillin, streptomycin and chloromycetin).[13] In a few tests Group A viruses have shown no susceptibility to aureomycin.[4b] They survive prolonged

TABLE 1. (*Concluded.*)

OTHER LABORATORY HOSTS (SUCKLING HAMSTERS)[1]	PHYSICAL CHARACTERISTICS						
	RESISTANCE TO DIETHYL ETHER	RESISTANCE TO ANTIBIOTICS[7, 13]	SIZE AS DETERMINED BY ULTRAFILTRATION (GRADOCOL MEMBRANES)	SIZE AS DETERMINED BY ULTRACENTRIFUGATION	SIZE AS DETERMINED BY ELECTRON MICROSCOPY	THERMAL DEATH POINT	pH VIABLE RANGE
			millimicrons	*millimicrons*	*millimicrons*	°C.	
Adapted to chick embryo[11, 12]; grown in tissue culture[12]; chimpanzee†[14]	+	+	—	36–37[26]	36–38[26]	53[27]	2.3–9.4[27]
None reported	+	+	—	—	—	51[27]	2.3–9.4[27]
Chimpanzee†[18]	+	+	15–23[20]				
Grown in tissue culture[15, 16]			10–15[21]	27, 28, 33[30]	35[26]	60[15]	—
Chimpanzee†[14]	+	+	—	—	—	—	—
Chimpanzee†[7]	+	+	—	—	—	—	—
Chimpanzee†[7]	+	+	—	36–38[26]	36–38[26]	—	—
Chimpanzee†[14]	+	+	—	—	—	—	—
Chimpanzee†[14]	+	+	10[27] 7–10[30] 10–15[21]	25, 28[30]	—	53[27]	2.3–9.4[27]

also for the viruses of poliomyelitis and murine encephalomyelitis. Since they can be grown with ease, large amounts of virus are readily available for purification and concentration. Several of the agents have been visualized in the electron microscope — revealing remarkably similar particles. One strain grown in both suckling mice and chick embryos revealed identical particles in both.[26] Calculations from electron-microscope pictures gave a particle size for all preparations of 36 to 38 millimicrons that was in close agreement with sedimentation values obtained in the ultracentrifuge with similar preparations of the same and similar agents.[26, 30] Gradocol filtration studies[20, 21, 27] have indicated that some of the particles may be smaller exposure to a wide range of pH values[27] and are inactivated only by temperatures as high as 51° to 60°C. or above for thirty minutes.[13, 27]

It is interesting that Type 1 virus differs from the others in Group A in the clinical picture produced in mice,[7] and represents one of the two types not yet associated with herpangina. Similarly, the B strains (Connecticut 5, Nancy and Powers B1, B3 and B4 respectively), which have been found in situations suggesting a causal role in epidemic pleurodynia, have comparable, but not identical, properties. All three appear able to produce infection and immune responses in adult mice whereas this capacity has not yet been demonstrated for the Ohio strain.

It should be emphasized that the clinical and pathological pictures that result from injection of these viruses into mice do not necessarily reflect those in man: in fact, the conditions produced in many laboratory animals by agents whose etiologic role in man is unquestioned are often entirely unlike those produced by the same agents in man, and serve only as a means of detection and recognition.

Diagnosis of Coxsackie Virus Infections

At present several procedures are available for the diagnosis of infection with the Coxsackie viruses. The method most frequently used is the isolation of virus in suckling mice from the feces, throat swabs, pharyngeal washings or anal swabs followed by immunologic typing of the virus strains. Confirmation of infection is obtained when an antibody rise is demonstrated against the homotypic strain in neutralization tests performed on serums from the infected persons.[4, 7, 51] Complement-fixation tests performed with human serums show, however, in many cases, heterotypic responses to virus types other than the one isolated from the patient.[51, 52] These heterotypic responses are often equal to or greater than the response to the homotypic virus. On the other hand, such heterotypic responses are observed rarely if at all when serums are tested for neutralizing antibodies. For this reason, the complement-fixation test is of little value in the diagnosis of human infections; the specificity of neutralizing antibodies, however, makes possible a serologic diagnosis of infection provided that suitable paired specimens are obtained. This procedure requires multiple viral reagents and is therefore too cumbersome for general diagnostic use. Furthermore, unless tests are performed against all available agents, a negative result has little meaning. Consequently, the diagnosis of Coxsackie virus infections remains, for the present, the prerogative of research laboratories equipped to attempt large-scale isolations and typing of virus. It must be emphasized that virus isolation and positive serologic tests by themselves indicate infection only and that accurate clinical and controlled epidemiologic observations are required before etiologic significance can be assigned to new viruses occurring concomitantly with clinical syndromes.

Table 2. *Current Knowledge of Some Attributes of 4 Immunologically Distinct Group B "Coxsackie Viruses."*

Virus Type	Illness in Man*	Suckling Mice				Adult Mice	
		Illness	Pathology			Illness	Pathology
			myositis	*central-nervous system*	*viscera*		
Connecticut 5[28] (B1)[28] (Demole)[29] (H. K.)[49]	Repeatedly associated with pleurodynia[29, 41, 42]	Larger doses produce short incubation, ataxia, cyanosis with fine tremors followed by death; smaller doses produce long incubation, convulsions and paralysis usually followed by death (occasional recovery).	Slight[17] or moderate†[10, 21]	Marked†[9, 17]	Pancreatitis Hepatitis Panniculitis Myocarditis†[10, 17, 21]	Loss of weight, hunched back, ruffled fur, death[18, 22]; asymptomatic infections.‡[18, 20]	Pancreatitis‡[17] necrosis of acinal cells.
Nancy[4] (B3)[28] (Washington 518)[43] (Texas pleurodynia)[36]	Repeatedly associated with pleurodynia[26, 43]		Slight[44]	Moderate[44]	Pancreatitis Hepatitis Panniculitis Myocarditis?[44]	Occasional death Asymptomatic infections[44, 45]	Pancreatitis[44] Necrosis of acinal cells
Powers[47] (B4)[28]	Associated with pleurodynia?[48]		None[17] or slight[10]	Moderate[17]	Pancreatitis Hepatitis Panniculitis Myocarditis[17]	Asymptomatic infections[44, 45]	To be studied
Ohio[28] (B2)[28]	Associated with summer grippe?[49]	Same as for other Group B immunologic types	Moderate[10, 17, 21]	Marked[17]	Hepatitis Panniculitis Pancreatitis Myocarditis[17]	Infection not known to occur	To be studied

*Practically all strains have been recovered from cases of clinical poliomyelitis — but their relation, if any, to this disease is obscure.

†Fuchsinophilic granules.[19]

‡Pathologic changes in pancreas; development of neutralizing and complement-fixing antibodies.

§Asymptomatic infections; fecal and oropharyngeal carrier states; viremia noted in some experiments; development of type-specific neutralizing and complement-fixing antibodies.

Epidemiology

The majority of the early reports concerned with Coxsackie virus infections have stressed their occurrence in pharyngeal secretions and feces of persons ill with clinical poliomyelitis. Unfortunately, the majority of these reports were made before it

was realized that the viruses occur in multiple immunologic types and represent possibly the most prevalent viral parasites of man (with the possible exception of influenza viruses). Consequently, few or no data were collected from other than highly special groups of sick persons; thus it cannot be concluded that the natural occurrence of these viruses is adequately reflected in most published reports. The distributions of Group A Coxsackie viruses as given in these reports, which have been discussed by us in a previous paper,[23] are briefly reviewed. The meager knowledge of the epidemiology of Group B viruses is also presented. Consideration is given, in general to the distribution of these viruses by several attributes; and in particular to their relation to disease.

Table 2. (*Concluded.*)

Other Laboratory Hosts	Physical Characteristics						
	Resistance to diethyl ether	Resistance to antibiotics[7, 13]	Size as determined by ultrafiltration (gradocol membranes)	Size as determined by ultracentrifugation	Size as determined by electron microscopy	Thermal death point	pH viable range
			millimicrons	*millimicrons*	*millimicrons*	*°C.*	
Chimpanzee§[13]	+	+	15–23[13, 30]	26, 28[30]	—	60[13] 53[37]	2.3–9.0[37]
None reported	+	+	—	—	36–37[46]	—	—
None reported	+	+	—	—	—	—	—
Cynomolgus monkey: fever, viremia, fecal and oropharyngeal carrier state[30]	+	+	15–23[13, 30]	27[30]	—	60[13] 51[37]	—
Chimpanzee§[13]							

Distribution in Nature

Coxsackie viruses of both Groups A and B are found in human excretions or secretions. The most common sources are human feces, and rectal swabs are thus feasible as survey tools.[23, 24] As might be expected, such coprophilic and resistant viruses have also been isolated from sewage[28, 53, 54] and flies.[28] Group A viruses may be isolated from human throat or nasopharyngeal washings,[3, 7, 23, 24, 32, 55] as may those of Group B.[28, 39] Reported isolations of Group A viruses from human blood, serum and central-nervous-system tissues at autopsy[3] have not been confirmed,[23, 56] and reason exists for doubting their validity.[3, 7, 23]

We have previously reported that Group A Coxsackie viruses, although occasionally recoverable from the feces for as long as forty-seven days or rarely for seventy-six days, had usually disappeared within a month of initial isolation. Melnick et al.[33] have recently reported a similar time limit for recovery of virus of Group A, Type 1.

No published work to date had shown reinfection of a single person with a single virus type, and serologic evidence of the development of protective, type-specific antibodies indicates that such a reinfection would be indeed unlikely.[57] On the other hand, it has been shown that a person may be successively infected with different immunologic types of Group A virus [23] or may simultaneously harbor two different Group A types[58] or a Group A and a Group B virus.[59] The greater percentage of adults having antibodies against increasing numbers of Group A Coxsackie viruses[57] suggests that such multiple experience with these viruses is common and increases with age. Dual infections with a Coxsackie virus and a poliomyelitis virus have been

repeatedly observed and are discussed below in relation to causation of illness.

Geographic Distribution

Coxsackie viruses are widely distributed throughout the world; it appears, in fact, that they have been isolated wherever attempts have been made. If Groups A and B are included together with ungrouped viruses, isolations have been reported in the literature from a total of 18 states in this country, and reports of many more isolations that have not yet been published are known. Isolations of Group A viruses are most common, having been reported from 13 states; Group B viruses have been found in 5 states, and ungrouped viruses in 2. In addition, Coxsackie viruses have been reported from Alaska,[60] Canada,[53, 61-64] England,[65, 66] France,[67-69] Denmark,[70] Holland,[48] Sweden,[71, 72] Israel,[73] Australia[54] and South Africa[74]: most of these are sporadic isolations, and many have not yet been identified, by either group or type, with strains recognized in the United States.

Distribution by Sex

Adequate studies that include data on the sex of persons tested for Coxsackie viruses are few. Dalldorf and Gifford[56] indicated a 2:1 ratio of males to females among persous positive for virus from nearly equal numbers of each sex tested; these results, however, were acquired from a cumulative experience of several years, from retrospective studies of stools, from epidemics in several different geographic areas, and apparently included isolations of Group A, Group B and unidentified viruses of several different types. In a study of the natural occurrence of Group A Coxsackie viruses among the inhabitants of a localized residential area, we found that the occurrence of illness and of virus was not influenced by sex differences.[23]

Distribution by Race

Data on the racial distribution of Coxsackie viruses are inadequate. It is obvious from the foreign reports that various, but most often unidentified, Coxsackie viruses may occur sporadically in persons of several nationalities — including, in addition to the diverse racial stocks of Americans, Swedish,[71, 72] French,[67-69] Dutch,[48] Danish,[70] English[65, 66] and Australian[54] and Israelis.[73] The racial backgrounds of these last are not known, but isolations have also been made from Alaskan Eskimos,[60] South African Bantu infants[74] and American Negroes[23, 24] and what is now recognized as herpangina occurred in Negroes in the outbreak reported by Levine et al.,[75] as well as in our series.[23, 24] We were not able to show, however, any predilection of Group A viruses for either whites or Negroes, isolations being obtained with insignificantly different frequencies from each group. From the available data, then, it does not appear that the distribution of Coxsackie viruses is influenced by race of the host.

Distribution by Age

Coxsackie viruses have been sporadically isolated from persons in nearly all age groups, varying from infants of one month of age to adults in the seventh decade of life. Systematic and large-scale investigations of the influence of age are, however, few. From most reports, a tendency for isolations to be more frequent in children emerges: in a previous study of the Group A viruses causing herpangina,[23] isolations were significantly more frequent in children under four years of age than in older persons. Accumulated experience in the literature seems to confirm the importance of age, but compilation of data in this way is hardly legitimate because of the dissimilarities of the studies reported, their variation in size, the lack of adequate control groups and the inclusion of studies on isolation of viruses of different groups and types.

Exposure

There is strong evidence for the importance of familial or household exposure in the acquisition of infections with Group A viruses.[23, 57] Observations on familial aggregation in cases of herpangina, on secondary infections and on the spread of herpangina among playmates indicated person-to-person transmission of the viruses. Serologic studies of the same population at the same time have shown that nearly all susceptible persons within a household become infected, once the virus is introduced, although all do not develop clinically apparent disease.[57] Only 1 case of probable sibling infection, based on antibody elevations to a Group A, Type 1, virus, has been reported by Melnick et al.[33]

Season

The majority of isolations of Coxsackie viruses of all groups have been made in summer and early fall months. This is largely because of the habit of examining stools from poliomyelitis or poliomyelitis-like diseases, which were collected only in these seasons. There is evidence, however, that at least one type of Coxsackie virus of Group A that was not present in a community in December or in the following June appeared and caused herpangina in July; in our experience in a single area over a fourteen-month period, Group A herpangina viruses were recovered significantly more often in August and September than in all other months combined.[23] It is likely, with year-around sampling, that occasional isolations will be made in other seasons: isolation of a single type, apparently persistent from August, was made in 1 patient of our series in December,[23] and Dahlstrom[71] has reported isolation of an unidentified Coxsackie virus in January in

Sweden. Isolations were made in South Africa in December, January and February,[74] but in that latitude this is the summer season. Two isolations of a new antigenic type were made in October or November in Northern Alaska.[60]

(To be concluded)

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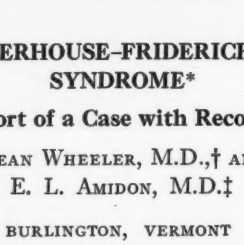
MEDICAL INTELLIGENCE



WATERHOUSE–FRIDERICHSEN SYNDROME*

Report of a Case with Recovery

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THE Waterhouse–Friderichsen syndrome is noted for its intensity, rapidity of progression and extremely grave prognosis. It was considered to be a universally fatal disease until 1940, when Carey[1] reported a case ending in recovery. Since then there have been recorded instances of recovery but the mortality remains extremely high. The few instances of recovery have tended to raise a question concerning the diagnosis and to bring up for review the pathological mechanisms of the disease. In addition, the treatment of the condition is far from standardized owing to the poor results obtained with present-day therapy.

The earliest pathological reports on the syndrome stressed the total obliteration of both adrenal glands by gross hemorrhages. Later, an occasional case was found in which only one adrenal gland was involved by hemorrhage, and in 1942 Williams[2] reported that 8 out of 17 patients examined had no, or only slight, hemorrhages in the adrenal glands. At first this led to the belief that the clinical course of the syndrome resulted from the fulminating sepsis and that the adrenal hemorrhage was only an incidental and secondary factor. However, with the increase in the knowledge of functions of the adrenal glands it is now seen that they play a primary role in the Waterhouse–Friderichsen syndrome. Zamcheck[3] showed that the adrenal glands undergo a series of morphologic changes associated with acute stress, but are absent in cases of sudden traumatic death. These characteristic adrenal changes consist of an increase in the size of the cortex, a loss of liquids from the outer cortical zones, transudates and inflammatory exudates into the cell columns and multiple scattered areas of thrombosis. Pseudotubule formation is common in the zona fasciculata and congestion, eventually leading to hemorrhages, which spread centrifugally from the zona reticulosis. Superimposed upon these changes are extensive hemorrhages, involving the cortex and occasionally the medulla in cases of menigococcal septicemia. The available store of adrenal hormone is quickly exhausted as in any acute stress reaction, and it is at just this time that the extensive hemorrhages from the meningococcemia take place. These hemorrhages occur in a gland that has already undergone severe cytologic changes. The adrenal glands are completely unable to supply any of their hormones just at a time when they are most needed. Thus, it is easy to see why the Waterhouse–Friderichsen syndrome is so devastating, and its associated collapse occurs with such speed and severity. From these observations it can be seen that immediate hormonal replacement in large quantities should be undertaken and continued until the adrenal glands have at least partially recovered.

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CASE REPORT

A 53-year-old woman had been perfectly well except for a cellulitis of the nose of 2 days' duration. She awoke at 2:00 a.m., complaining of severe pain in the thighs and calves. She was treated with sedatives and slept until 11:00 a.m. the following morning. At that time she became irrational and was apparently suffering from great pain in the lumbar area of the back and in the legs. The temperature was 105°F. by mouth. Sedation was repeated, but she immediately vomited the medication. Hospitalization was advised and she was admitted to the Mary Fletcher Hospital at 1:45 p.m. of the same day (October 4, 1951).

Physical examination revealed an acutely and severely ill patient who was semiconscious and delirious, with marked cyanosis of the face and all four extremities. A dusky-red indurated area covered the tip of the nose, with a fissure extending from the right naris up over the end of the nose. No petechiae were seen. There were about a dozen purpuric spots over the left side of the abdomen averaging about 1 cm. in diameter. They did not fade on pressure. The pharynx appeared perfectly normal. The chest was completely normal on physical examination, and neither focal neurologic nor meningeal signs were present.

The temperature was 106.8°F. by mouth, the pulse was weak and thready at a rate of 120 a minute, and the respirations were shallow and stertorous at a rate of 30 a minute. The blood pressure was 40/30.

Lumbar puncture yielded a clear spinal fluid initially, and a slightly cloudy fluid was obtained after a sudden movement

by the patient. While the spinal tap was being done petechiae were seen appearing over the entire back. These petechiae rapidly enlarged and formed purpuric blotches. When the patient was returned to the supine position it was observed that her entire body was covered with hemorrhagic lesions. Examination of the spinal fluid showed a total protein of 54.8 mg. per 100 cc. and total cells of 2312 per cubic millimeter, the white cells being 2 per cubic millimeter; the Pandy test was positive. No organisms were found on smear or culture. Cultures of the throat, purpuric lesions and nose were negative. Blood culture, however, revealed *Neisseria meningitidis*.

Examination of the blood disclosed a red-cell count of 4,120,000, with a hemoglobin of 14 gm. per 100 cc., and a white-cell count of 5000, with 50 per cent neutrophils, 18 per cent stab forms, 29 per cent lymphocytes and 3 per cent myelocytes (there was severe toxic degeneration of 100 per cent of the neutrophils). The eosinophil count was 25 per cubic millimeter. The blood sugar was 107 mg., the nonprotein nitrogen 42 mg., and the total protein 5.90 gm. per 100 cc. with 3.28 gm. of albumin and 2.62 gm. of globulin. A Foley catheter was inserted, yielding 150 cc. of normal urine.

Therapy was immediately instituted, consisting of an infusion of 5 per cent glucose in physiologic saline solution, 100,000 units of crystalline penicillin intramuscularly every 4 hours, 500 mg. of aureomycin intravenously every 6 hours, 50 mg. of cortisone intramuscularly every 6 hours, and aqueous adrenocortical extract, 10 cc. intravenously every 2 hours. In addition, during the next few hours the patient was given intravenously 850 cc. of whole blood, 300 cc. of plasma and 1000 cc. of 5 per cent glucose in distilled water. In an attempt to raise the blood pressure, epinephrine in oil was also given, 1 cc. (2.0 mg.) intramuscularly every 4 hours. The patient's condition did not change, and the blood pressure remained about 50/30. The urinary output from admission until midnight was only 15 cc.

On the 2d day the patient started vomiting, and consequently duodenal drainage was established, with no improvement whatsoever in her status; desoxycorticosterone acetate was given (10 mg. intramuscularly twice on October 5 and 5 mg. once on October 6). The dosage of aqueous adrenocortical extract was increased to 30 cc. intravenously every 2 hours. When she was placed in an oxygen tent the cyanosis lessened, and restlessness decreased.

On October 6 the blood pressure started to rise, reaching 85/50. The urinary output increased to a 24-hour total of 330 cc. She was moderately overhydrated, as shown by slight peripheral edema and serum chloride of 96.2 milliequiv., sodium of 122.5 milliequiv. and potassium of 2.95 milliequiv. per liter, and a hematocrit of 36.5 per cent. The fluid intake was restricted, and 30 milliequiv. of potassium was added to the intravenously administered fluids. The patient started retaining small amounts of fluids by mouth. The duodenal suction was stopped, and she was passing gas by rectum. The aqueous adrenocortical extract was replaced by Lipo-adrenal cortex, which was given as 1 cc. intramuscularly every 4 hours.

By October 7, she was greatly improved, alert and fully conscious for the first time. The blood pressure was up to 120/85, and the urinary output for that day was 3040 cc. A moderate deficiency of potassium developed, as shown by an electrocardiogram and a serum potassium of 3.3 milliequiv. per liter; the serum sodium at that time was 145.0 milliequiv. per liter. This deficiency was treated with intravenously administered potassium and fluids by mouth. From this point onward the patient's condition continued to improve. The skin lesions rapidly cleared, with the exception of the larger ones, which underwent necrosis, with sloughing and hence delayed healing. On October 8, slight jaundice developed, and consequently aureomycin therapy was discontinued. A severe infection of the mouth gradually appeared; antibiotic therapy was therefore stopped. The dosages of all medications were gradually reduced and eventually discontinued. Cortisone was discontinued on October 12. The total endocrine therapy consisted of 900 mg. of cortisone, 670 cc. of aqueous adrenocortical extract, 15 cc. of Lipo-adrenal cortex extract, 15 mg. of desoxycorticosterone acetate and 29.5 mg. of epinephrine. During convalescence an ACTH test was given, and a 23 per cent drop in eosinophils occurred in 4 hours (initial count, 86, and 4-hour count, 62). A week later a second ACTH test was done, with a resulting eosinophil drop of 27 per cent (initial, 118, and final count, 86). A final ACTH test, done 6 weeks after cessation of cortisone therapy, showed a 35 per cent drop in the eosinophil count, at the same time that the uric acid creatinine ratio increased only 25 per cent after injection of ACTH.

Discussion

In this case of fulminating menigococcal septicemia complicated by profound collapse, anuria and purpura (the syndrome described by Waterhouse and Friderichsen), the adrenal glands were damaged and this damage was a major factor in the pathogenesis of the syndrome, as shown by recovery when large doses of adrenal-hormone preparations were used and by the ACTH test, conducted during the convalescent period, which demonstrated a drop in the eosinophil count of only 23 per cent, 27 per cent and 35 per cent, as well as an increase in the uric acid creatinine ratio of only 25 per cent.

It is of interest that the first eosinophil count was 25 per cent. This count was taken shortly after admission, when the patient was in severe shock, with a temperature 106.8°F., a developing purpuric rash and comatose. It appears that the adrenal response was adequate from this eosinophil count, according to Thorn.[4, 5] However from the subsequent course and from the ACTH test done during convalescence, it seems that such an inference could not be drawn in this case. Because of the extremely fulminating course of the disease the eosinophil count may have been 0 for a short time and we obtained our count just as the eosinophils started to increase. Furthermore, the lower the eosinophil count the greater the likelihood of error by the laboratory, with a resulting decrease in reliability of the test. We therefore believe that although the eosinophil count is of value in acute adrenal insufficiency it is not diagnostic and should not overrule a clinical evaluation of the patient.

In 2 cases recently reported by Nelson and Goldstein[6] immediate improvement was noted after cortisone therapy was initiated, whereas no response had been seen after the administration of whole adrenocortical extract. In the case reported above cortisone was used from the first along with whole aqueous extract and desoxycorticosterone, with no apparent improvement up to about sixty hours. It seems to us that no statement about the efficiency of any one of these preparations can be made at present, but that they should be used simultaneously and in large quantities. In addition in this patient several complications developed during the recovery period, demonstrating some previously noted facts. The first is the tendency for fungous and yeast infections to appear when the patient is receiving large doses of antibiotics. (In our patient a severe infection of the mouth and throat developed from a nonpathogenic yeast.) The second is the development of jaundice during daily treatment with more than 1.0 gm. of aureomycin intravenously.

(Our patient was given 2 gm. of aureomycin intravenously daily and mild jaundice developed on the fourth day of treatment; of course, we cannot rule out the possibility that the original disease with its resultant severe and prolonged state of shock did not cause the liver damage.) The third is the occurrence of hypopotassemia in the patient being treated with adrenocortical hormones (this phenomenon occurred in our patient during the stage of increased urinary output following some sixty hours of anuria).

Summary

A case of Waterhouse–Friderichsen syndrome with recovery is presented.

The eosinophil count is of value in cases of acute adrenal insufficiency but is not diagnostic and is not always a true indication for specific therapy.

All available adrenal hormone preparations should be used simultaneously in addition to antibiotics and symptomatic forms of therapy in the treatment of this condition.

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Massachusetts Physicians Art Association

7. Market Day.

(*Exhibited at Annual Meeting of the Massachusetts Medical Society 1950*)

Oil Painting by

Joseph A. Lundy, M.D.

Physician to the Worcester City and Hahnemann Hospitals

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38331

PRESENTATION OF CASE

First admission. An eight-and-a-half-year-old girl was admitted to the hospital because of a swelling in the neck.

Seven months before entry the patient's mother noticed an increase in the patient's weight without increase in the food intake. The child became lethargic, tired easily and was very irritable. The hair became coarse, the eyebrows and eyelashes sparse, and the skin thickened, yellow and "sandpapery." She complained of leg pains and of sensitivity to cold. About the same time a swelling in the neck, which grew to the size of half an egg, was noted. Five months before admission the patient was started on thyroid; within two weeks the symptoms began to abate, gradually disappearing except for the skin changes. The swelling in the neck was said to have regressed while she was on treatment. Six weeks before entry the thyroid medication was stopped, all the symptoms recurred, and there was rapid enlargement of the swelling in the neck.

The birth and developmental history were normal. The patient was in the third grade in school. She had an appendectomy at the age of seven, and at seven and a half pneumonia of "both lobes," which was treated with sulfadiazine. There was no history of infection or fever immediately preceding the present illness. She had taken Calcidin and iodine as an expectorant when she had pneumonia, and Benadryl periodically for mild asthma. There had been no other medications. She had lived in New England all her life.

The father and a paternal aunt had food allergies, but there were no other family diseases.

Physical examination revealed a well developed, well nourished girl weighing 63 pounds and measuring 49 inches in height. The skin and hair were dry and coarse. There was a left-sixth-cranial-nerve paralysis. The thyroid gland was enlarged to three or four times its normal size; the right lobe was larger than the left. Its surface did not appear to be definitely nodular. A small Delphian node was barely palpable in the midline. Bruit and thrills were absent. There was a soft blowing systolic murmur in the pulmonic area, and the remainder of the findings were normal.

The temperature was 98.6°F., the pulse 88, and the respirations 20; the blood pressure was 90 systolic, 65 diastolic.

The urine was acid, had a specific gravity of 1.024 and gave a + reaction for albumin; the sediment contained 35 white cells per high-power field. The hemoglobin was 12.8 gm., and the white-cell count 9300, with a normal differential. The blood cholesterol was 410 mg. per 100 cc. The tuberculin test was negative. The uptake of radioactive iodine was slow and at a low level. Roentgenograms of the skeleton showed a bone age of seven years and three months. A chest film was normal. A barium-swallow examination demonstrated a soft-tissue swelling anterior to the trachea corresponding to the palpable goiter. The trachea appeared to be somewhat narrowed in the lower part of the neck but was not displaced. There was no evidence of retrosternal extension.

The patient remained in the hospital for two days and was discharged to take 30 mg. *U.S.P.* thyroid a day at the start, with gradual increases depending on her tolerance.

Second admission (four months later). In the interval the patient had continued on thyroid medication. The dose had gradually been increased to 130 mg. a day, and then three weeks before admission had been reduced to 100 mg. because of "overexuberance." Her appetite had not improved. Muscle aches, especially in the thighs, calves and back, were present. Her mother noted that she tired easily.

Physical examination revealed a 2-pound weight loss. The thyroid gland had increased slightly in size. The heart murmur was no longer heard. Otherwise the findings were unchanged.

She was discharged after three days in the hospital, to continue with the thyroid medication.

Final admission (seven months later). In the interval the patient's physical condition remained unchanged. She had continued on the thyroid medication. She was readmitted for further evaluation.

Physical examination revealed a happy, seemingly well adjusted girl, in no distress. The thyroid gland was diffusely enlarged, with numerous semidiscrete, rubbery, nonfixed nodules palpable on the surface. The entire mass was estimated to measure 6 by 5 by 4 cm. and was visible. The remainder of the examination was negative. On the third hospital day an operation was performed.

Differential Diagnosis

Dr. Jacob Lerman*: "The uptake of radioactive iodine was slow and at a low level." This is a peculiar way of reporting the uptake of radioactive iodine, unless someone was doing gradient studies.

Dr. Austin L. Vickery: That is the way the iodine uptake was reported in the record. I tried to find out more specific information about it. This girl came into the hospital on a number of occasions but did not stay long enough for urine-excretion studies; apparently, merely a scanning procedure was done.

Dr. Lerman: She did not receive thiocyanate after the initial dose of radioactive iodine.

Dr. Vickery: No; she did not. The uptake of radioactive iodine was always low; one would have liked to have a forty-eight-hour uptake if this could have been arranged.

Dr. Lerman: May I see the x-ray films.

Dr. Stanley M. Wyman: I do not think the x-ray films add much to the report in the protocol. The soft-tissue swelling in the neck can be well seen in the lateral view of the neck, compressing the trachea slightly.

Dr. Lerman: The description of the patient given in the first two paragraphs is quite characteristic of a youngster with juvenile myxedema. This diagnosis, which I shall accept clinically, was verified later by the laboratory findings of a low uptake of radioactive iodine, a high cholesterol and the satisfactory response to thyroid. When a goiter associated with myxedema shrinks while the patient is receiving thyroid medication, one has to think of three main types of goiter. The first is struma medicamentosa, such as goiters associated with myxedema resulting from sulfonamides, the thiouracil group of compounds and thiocyanate. Perhaps Benadryl is a goitrogen. Another type of goiter, also associated with myxedema, is that resulting from the ingestion of food goitrogens, such as cabbage, rape seeds and certain types of beets. This patient gave no history of ingesting any of these goitrogens. The third type is struma lymphomatosa, or Hashimoto's struma. We have seen several such patients whose thyroid glands have shrunk when thyroid was given to them. I should include the nodular type of goiter seen in sporadic cretinism, which also may shrink on the administration of thyroid. Patients with this type of goiter do not have juvenile myxedema; the patient under discussion was normal up to a certain age and then developed myxedema. My colleagues and I[1] have studied this type of goiter at various times and have shown that it takes up iodine but contains very little organic iodine. In addition Stanbury and Hedge[2] demonstrated that it has the peculiar property of being able to trap iodine but unable to convert it into hormone; the iodine is released on the administration of thiocyanate. It is this inability to convert iodine into hormone that causes myxedema.

A bizarre occurrence was that, on readministration of thyroid, the goiter did not shrink but actually increased in size.

Dr. Vickery: Apparently, there was some difference of opinion among the various observers about that finding during the last admission; some thought it was smaller, some that it was about the same size, and still others that it had increased in size.

Dr. Lerman: That tends to rule out such conditions as struma medicamentosa, and struma cibaria, due to food ingestion, which tend to shrink on the administration of thyroid. Our experience has been that struma lymphomatosa, although it may shrink during the administration of thyroid, may not shrink entirely; there is always some residual swelling.

A large goiter due to iodine deficiency is a possibility, but in this part of the country is not associated with myxedema. Can this have been the type of goiter seen in patients who have long-standing hyperplasia? In sporadic cretinism, involutional changes take place, developing papillary formations, hyperplasia, struma microfolliculari and macrofolliculari and even areas that cannot be distinguished from fetal adenoma.

Although I think there is a possibility that in long-standing hyperplasia, neoplastic changes can develop, it is true that we have not seen a single case in which it has been proved that neoplasia has developed in long-standing hyperplasia of the thyroid gland. Experimentally, it has been demonstrated several times that in animals undergoing stimulation of one form or another the thyroid gland first becomes hyperplastic and sooner or later develops malignant changes with or without the presence of a carcinogen. It would be news to find that, in human beings, hyperplastic glands had undergone malignant degeneration.

I am reluctant to accept the possibility of cancer because myxedema is not associated with cancer of the thyroid gland. When a goiter is associated with myxedema, a good clinical rule is that one can almost always rule out carcinoma — I say "almost" because there are exceptions to any rule. Carcinoma does not destroy the thyroid gland completely and therefore does not produce myxedema. A carcinomatous thyroid gland does not shrink upon the administration of thyroid.

I prefer to believe this patient had a large nodular goiter resulting from hyperplasia, as a first choice, struma lymphomatosa as a second choice, and papillary adenocarcinoma resulting from malignant degeneration of a hyperplastic gland as a remote possibility.

Dr. John T. Stanbury: We have seen several patients from time to time who have had very large goiters that took up iodide extremely rapidly and to

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a high final level. It was with that in mind that we were studying this patient, who was obviously hypothyroid and had a goiter. However, the accumulation of I^{131} in the gland was very slight. Although we did not determine the forty-eight-hour uptake or excretion because the patient was not able to return, we could be sure from a few hours of observation that the uptake was extremely low — probably 10 per cent at the most. Since the patient did not fall into the group of high I^{131} uptake with goiter and hypothyroidism, we believed that she had Hashimoto's thyroiditis. It was with this in mind that she was given desiccated thyroid to more than tolerance and then dropped back. There was a considerable difference of opinion about whether the goiter changed in size. I thought it was larger; Dr. Oliver Cope thought it was slightly smaller. It probably did not change much in size, at any rate; it is always difficult to remember six months afterwards how a gland felt. I do not think the reaction of a Hashimoto's struma to administered thyroid is necessarily uniform. We have seen patients whose glands have increased in size unquestionably while on large doses of thyroid. I think it is still debatable whether desiccated thyroid consistently causes regression of Hashimoto's thyroiditis.

Dr. Vickery: In the cases of Hashimoto's struma that were reviewed here[3] there was evidence that some of the patients who were given a course of thyroid had not been taking the drug faithfully; I think the opinion was that those glands comprised a fair number of the so-called failures to regress in size, although I think everybody would agree that the issue is unsettled.

Dr. Lerman: If I could be sure that the patient's gland had decreased in size, I would say that Hashimoto's struma was the most likely diagnosis. No variation in size would not help me much. Ordinary nodular goiter does not change with thyroid whereas Hashimoto's struma does under certain conditions.

Dr. Stanbury: I am not sure I can agree with that as a blanket generalization. The iodide-deficient nodular goiter may diminish markedly in size on thyroid medication.

Dr. Lerman: I am referring to a nonendemic area here.

Clinical Diagnosis

Hashimoto's struma.

Dr. Lerman's Diagnoses

Nodular goiter.
?Struma lymphomatosa.
?Papillary adenocarcinoma in long-standing hyperplasia.

Anatomical Diagnosis

Struma lymphomatosa (Hashimoto's struma) in an eight-and-a-half-year-old girl.

Pathological Discussion

Dr. Vickery: At operation Dr. Cope exposed a diffuse goiter with a lobulated surface nonadherent to adjacent structures that had a uniformly firm consistence; his impression was that it was probably thyroiditis. Frozen section of a biopsy taken from the larger lobe confirmed the diagnosis of Hashimoto's struma.

The thyroid weighed 35 gm., which is about three times what it should weigh in a girl of this age. Grossly, the surface of the gland was gently lobulated; such lobulations often give the clinical impression that the thyroid gland is nodular; on cut section the lobulations are not distinct nodules but very accentuated lobules of the gland. The thyroid gland had a strikingly homogenous appearance, which is seen in nearly all cases of this condition — a pale yellowish-pink surface, with obliteration of all normal thyroid tissue. Microscopically, there were no remaining normal follicles within either of the lobes, and the parenchyma showed marked atrophy. The impressive feature was the diffuse dense infiltration with lymphoid tissue, many actual lymphoid follicles being present.

The etiology of this disease has frequently been discussed; suffice it to say that nobody knows precisely what the etiology is. There is some evidence that it is endogenous in the form of an endocrinopathy rather than exogenous from a toxic substance or an infectious agent. I believe that Dr. Lerman, who has a special interest in this disease, would agree that one possibility that has not been completely explored is a viral etiologic agent. I think it is unlikely, but nonetheless that has not been completely ruled out.

This girl, being eight-and-a-half years of age, represents as far as I know the youngest case that has been reported with Hashimoto's struma. In the past, we have analyzed 51 cases of this disease seen in this hospital over a twenty-year period[3] and grouped them according to physiologic age. There were 2 of age ten and 1 of age fourteen in this series. The average age of the females with this disease, which is one almost exclusively of the female sex, is about forty-three. Some physicians have used this average age as evidence that the disease was perhaps related to the menopause. The number of cases we have seen in this hospital of women actually in the reproductive stage of life and also of children seems more or less to obviate that possibility.

Dr. Myles P. Baker: What is thought about x-ray treatment for this condition?

Dr. Vickery: In the past the general treatment has been subtotal thyroidectomy largely because exploration was carried out to substantiate the diagnosis in most cases and it was considered wise to remove most of the thyroid gland at the same time. The alternative x-ray treatment has been used,

reportedly with good success, particularly in the Cleveland Clinic.[4] X-ray treatment has been given here in some cases; I think that the weight of opinion is that establishing the histologic diagnosis is the important thing and that, once the gland is exposed, it may as well be removed.

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CASE 38332

Presentation of Case

A sixty-eight-year-old business woman was admitted to the hospital because of mental confusion.

About one month prior to admission, the patient was observed by her family to be slightly "confused" at times; nevertheless, she was able to carry on her millinery business successfully. Four days before entry she seemed unable to answer questions put to her, and complained of a severe headache. On the following day she was unable to tabulate her sales slips correctly and appeared not to understand their significance, although she could speak without difficulty. In the two days before entry, she was again unable to answer questions and was speechless for a short time. Simultaneously, it was seen that she had a variable degree of difficulty in moving the right arm, most marked during the period of speechlessness. There was no recurrence of the headache.

One year before admission the patient had a routine physical examination and was told that her blood pressure was normal. The past history was characterized by excellent general health.

Physical examination showed a woman lying quietly in bed, incontinent of urine. Occasionally, she answered "yes" or "no" appropriately to simple questions, but did not speak otherwise, and did not obey simple commands. She showed no signs of recognition of her family when they came in. The neck was markedly stiff on forward flexion. The ocular fundi were normal. There was unimpaired vision and no apparent visual-field defect. The pupils were 3 mm. and reacted briskly to light. The cranial nerves were otherwise normal. Both arms were flexed at the elbow and wrist. The left arm moved fairly well, but the right arm was for the most part motionless. There was jerky tremulous resistance to passive stretching of flexors of the right elbow and wrist. The legs were strongly extended bilaterally and did not move except for flexion withdrawal to pinprick. The jaw jerk and other tendon reflexes were very brisk bilaterally, except for rather weak ankle jerks, and were generally somewhat more active on the right than the left. The plantar reflexes were extensor bilaterally, more strongly so on the right. There was no sensory impairment to pinprick. The physical examination was otherwise unremarkable.

The temperature was 101°F., the pulse 70, and the respirations 30. The blood pressure was 190 systolic, 92 diastolic.

Urinalysis was negative. Examination of the blood revealed a white-cell count of 12,400, with 83 per cent neutrophils, 13 per cent lymphocytes and 4 per cent monocytes, normal red cells and platelets in the smear and a hemoglobin of 13.4 gm. The nonprotein nitrogen was 28 mg. per 100 cc. A lumbar puncture on admission showed clear fluid under a pressure equivalent to 185 mm. of water; the fluid contained 4 lymphocytes per cubic millimeter and a total protein of 210 mg. per 100 cc. A lumbar puncture on the following day revealed clear fluid under a pressure of 240 mm. containing 6 neutrophils and 6 lymphocytes per cubic millimeter with a total protein of 112 mg. per 100 cc. A third lumbar puncture on the day before discharge showed a pressure equivalent to 200 mm. of water, with 3 lymphocytes per cubic millimeter and a total protein of 116 mg. per 100 cc.

An electroencephalogram on the third hospital day was grossly and diffusely abnormal, with generalized slow activity most marked in the left central and midtemporal regions. A second electroencephalogram at the time of discharge was likewise diffusely abnormal, slightly more so on the right, although more normal activity was seen (in the occipital region) than in the previous record.

Skull films showed hyperostosis of the inner tables of both frontal bones and, in the left frontal region superiorly, a mottled radiolucent pattern with some irregularity of the outer table in this region. The dorsum sellae was slightly thin. The pineal body could not be visualized.

On the second hospital day, the patient's rectal temperature rose to 104°F., with respirations ranging from 20 to 35, although the pulse remained steady at 80 per minute. The temperature gradually fell to normal in the next three days, and the respirations became irregular. The state of responsiveness meanwhile deteriorated from the time of admission until the third hospital day, when she lay in bed with eyes closed and made no sound. At times, however, she opened her eyes and looked at people that came near her. The neurologic findings were as before. On the following day she was conscious, alert, oriented and able to co-operate on testing. The right arm and leg were somewhat weaker than the left at this time, but three days later, and on subsequent examination, no definite weakness or spasticity could be found. The stiffness of the neck disappeared. She was able to speak clearly, with good use of words, was cheerful and unconcerned and denied any symptoms. She was continuously

incontinent of urine and feces. Simple commands were quickly carried out, but she failed to comprehend slightly more complicated instructions, and could not perform the simplest arithmetical problems. The plantar reflexes were repeatedly extensor bilaterally. During her last week in the hospital she again became disoriented, and her general state of responsiveness became slightly less than it had been, but she still was alert and co-operative and no new neurologic findings appeared. She was discharged on the thirteenth hospital day to the care of her physician.

During the first two weeks at home she was able to get up from bed to chair with assistance although she remained somewhat confused and incontinent of urine and feces. She soon developed progressive spasticity of the legs, and by the end of the third week she was completely paraplegic; she was able to move her upper extremities. Examination at this time, except for the paraplegia and absent tendon reflexes in the legs, revealed essentially the same findings as on discharge. Lumbar puncture showed a clear spinal fluid under a pressure equivalent to 185 mm. of water; the fluid contained 72 mg. per 100 cc. of protein and no cells. During this time, although on crystacillin therapy, she had several temperature elevations up to 102°F., after which the temperature gradually returned to normal over the subsequent few days. In addition she had two episodes of dyspnea during which she coughed up bloody sputum.

She went progressively downhill and died fifty-six days after discharge from the hospital.

Differential Diagnosis

Dr. Raymond A. Adams*: This sixty-eight-year-old woman had an illness that came on insidiously with episodes of mental confusion; caused a profound dementia, an episode of decerebrate rigidity, spasticity of the lower extremities, incontinence of urine and feces; and led to her death in a period of about three months. She also had several febrile periods, two episodes of dyspnea with hemoptysis, a leukocytosis and an abnormal spinal fluid.

Several points in the history are of interest. First of all, four days before admission her condition became definitely worse. She developed difficulty in understanding what was said to her and the significance of written material, but was able to speak without difficulty. I should interpret this as an aphasic disorder. She also had a brief attack of severe headache. This was followed by a period of speechlessness and of difficulty in moving the right arm, apparently without any involuntary movement. This points to a lesion of the left cerebral hemisphere. Her blood pressure, which was slightly elevated at the time of admission, was normal one year previously.

*Clinical fellow in neurology, Massachusetts General Hospital.

Examination showed that the patient was in a posture of decorticate rigidity, with the arms flexed at the elbow and wrist, the legs extended, and the neck stiff. This type of posture may occur with lesions of the upper brain stem, but it does not mean that the primary process is in that location. It may be seen with supratentorial lesions such as tumor that cause herniation of the uncus and hippocampal gyrus through the tentorium, with resulting compression of the midbrain. Other signs that are often present are fever, rapid pulse and respiration, dilatation of one or both pupils and impairment of consciousness. This condition may occur in attacks or lead to the death of the patient within a short time.

With the degree of mental confusion that existed, it is not surprising that the patient had incontinence of urine and feces, but this also occurs in cases of cerebral lesions with less pronounced confusion when the lesion is located in the paracentral lobules.

On the fourth hospital day considerable improvement occurred. However, the patient was still demented, and although she had incontinence of urine and feces. was unconcerned and denied any symptoms. Examination showed bilateral extensor plantar responses. These findings are those of bilateral disease of the frontal lobes.

About eight weeks after the onset of symptoms the patient developed progressive spasticity of the legs but was able to move her arms. Under these circumstances the paralysis of the legs could have been due to a lesion of the thoracic portion of the spinal cord or the paracentral areas of the frontal lobes. One of the most common causes of progressive spastic paralysis of the lower extremities is compression of the spinal cord. No other symptoms of diseases that cause this condition are given, and it can be excluded on the basis of the last lumbar puncture, which showed a spinal-fluid pressure equivalent to 185 mm. of water and a clear fluid containing 72 mg. per 100 cc. of protein. A compressive lesion of sufficient degree to cause paraplegia would be accompanied by a lower spinal-fluid pressure and a higher protein content of the fluid. But this does not exclude the presence of lesions within the substance of the spinal cord.

In this case the electroencephalograms were grossly and diffusely abnormal. May I see them, Dr. Schwab?

Dr. Robert S. Schwab: Two electroencephalograms were done and were essentially alike. This, the second one, shows slow activity in all leads but most markedly in the right and left frontal regions. It would not be accurate to say there is any significant difference between the two sides. I would say that both records show diffuse bilateral abnormalities more marked in the frontal region, which suggest a deep large lesion that is not on the surface of the cortex, or involvement of both frontal lobes.

DR. ADAMS: The x-ray films of the skull show, in addition to hyperostosis of the inner tables of the frontal bones, which occurs in a small percentage of normal skulls, an area suggesting a lesion in the left frontal region superiorly.

May I see the x-ray films of the skull?

DR. STANLEY M. WYMAN: There is an extensive area of bone abnormality in the frontal bone extending from a point above the frontal sinus well back beyond the coronary suture. It is chiefly left sided in location, and there is a suggestion that the calcified falx is displaced a very slight degree toward the opposite side. This lesion is well seen in stereoscopy, and there seem to be some perforating vessels going through this area of bone, which is definitely thickened and abnormally dense. I am not too impressed by any great degree of internal hyperostosis. I think it is more in the bone itself than in the inner table as one sees it in characteristic hyperostosis frontalis interna.

DR. ADAMS: When one considers the age of this patient, the gradual onset of her illness, the clinical course with death occurring after a period of three months and some of the other features of the case, the diagnosis of a malignant neoplasm of the frontal lobes is suggested. This could be a glioblastoma multiforme, a primary lymphoma or a metastatic carcinoma. The spinal-fluid findings are compatible with any of these conditions. Of these the least likely appears to be glioblastoma multiforme. A primary malignant lymphoma, either reticulum-cell sarcoma or Hodgkin's disease, is a rare condition and is usually diagnosed clinically as glioblastoma multiforme. Cerebral metastasis from carcinoma of the lung is a common occurrence. The metastatic lesions of these tumors often cause symptoms before there is any evidence of pulmonary disease. A bronchogenic carcinoma could also account for the two episodes of dyspnea and hemoptysis that occurred.

However, the absence of recurrent headache, papilledema and convulsions is against the diagnosis of tumor though it is well known that these symptoms may not always be present. Furthermore, there is evidence of disease of the brain and the upper brain stem and possibly also of the spinal cord and peripheral nerves. Peripheral nerve damage is suggested by the disappearance of reflexes in the lower extremities after spastic paraplegia had been present. The blood pressure was slightly elevated. The spinal fluid showed a definite fall in the total protein content from its original level of 210 mg. and disappearance of neutrophils and lymphocytes. This suggests that the central-nervous-system disease was becoming less active, but at a time when the patient was continuing to go downhill. This patient also had several febrile episodes without other physical signs of infection. In addition, the presence of pulmonary disease is shown by the occurrence of episodes of dyspnea and hemoptysis. The white-cell count was 12,400, with 83 per cent neutrophils. These findings indicate a pathologic process capable of involving different levels of the nervous system as well as other systems of the body. I believe, therefore, that this patient may have had polyarteritis nodosa, although malignant brain tumor chiefly involving the frontal lobes cannot be ruled out.

DR. WYMAN: What do you think the bone lesions were, Dr. Adams?

DR. ADAMS: I do not believe that they can be correlated with the various clinical manifestations of the patient's illness.

DR. BENJAMIN CASTLEMAN: Dr. Richardson, would you discuss the clinical aspects of the case?

DR. EDWARD P. RICHARDSON, JR.: This case presented a considerable problem. It was evident that something had happened to this patient very rapidly: within a matter of days she had turned from a person who was able to manage her business into one unable to understand her own sales slips, with episodes of speechlessness and transitory weakness of the right arm. In the hospital her condition deteriorated further. When I saw her on the second hospital day, she was in a condition resembling decorticate rigidity. Two days later there was a really dramatic improvement, in that the signs in the limbs disappeared and no further weakness whatsoever could be ascertained. Furthermore she had become able to carry on a fairly rational conversation. although it was apparent that her ability to comprehend was considerably reduced. She maintained this improvement for about two days and then toward the end of the hospital stay became slightly less responsive, without the appearance of new neurologic findings. This indicated that the process was still active, and was a point against bilateral frontal-lobe infarction from thrombosis of anterior cerebral arteries, as had been considered, for the natural course of uncomplicated cerebral infarction is one of continued improvement. Thus, it was thought at the time of discharge that the patient's entire illness could be explained on the basis of a rapidly growing infiltrating tumor involving the corpus callosum anteriorly and both frontal lobes and that the improvement might have been the result of infarction necrosis within the tumor mass itself, tending to reduce temporarily its size. She was discharged home without further study or operation at the desire of the family. The progressive downhill course at home is characteristic of neoplasm.

DR. WILLIAM H. SWEET: By a curious coincidence, Dr. Hannibal Hamlin and I have seen two other patients within the last six months in whom a rather abrupt onset of neurologic signs and symptoms was followed by a rather rapid subsidence of these signs and symptoms, and in both these patients the lesion turned out to be a neoplasm. In the first case, we did not make the diagnosis in

SEP 9 MANHATTAN KANSAS

vivo; when the second came along, we did and removed a cystic neoplasm in the cerebellar hemisphere. When this patient appeared I was by that time sensitized to the possibility that patients with intracranial tumors can improve strikingly after abrupt development of signs and symptoms, so that I was inclined, especially in view of the high total protein in the spinal fluid here, to think of the possibility of neoplasm in this case as well.

DR. J. T. HEYL: What did the radiologists think?

DR. WYMAN: We thought it might represent a meningioma from the suggestive air studies: we thought there were signs of chronic increased intracranial pressure.

CLINICAL DIAGNOSIS

?Brain tumor.
?Thrombosis, left anterior cerebral arteries.

DR. ADAMS'S DIAGNOSIS

Polyarteritis nodosa.

ANATOMICAL DIAGNOSIS

Glioblastoma multiforme of corpus callosum and both frontal lobes, necrotic.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy here was limited to examination of the head, which Dr. Richardson will tell you about.

DR. RHETT TALBERT: Dr. Richardson, how would you explain the rapid improvement on the basis of a frontal-lobe tumor?

DR. RICHARDSON: It is difficult to explain; I think the post-mortem findings will give some clue.

At autopsy, there was thickening of the frontal bone of the skull bilaterally, more marked on the left, but the bone appeared perfectly normal; we interpreted these findings as an anatomic variation. The appearance of the brain can be illustrated best by a photograph of serial coronal sections (Fig. 1). There is a large tumor, appearing first as a large outcropping on the surface of the right frontal lobe. Close examination of the left frontal lobe shows widening of the gyri, the result of involvement of the cortex by tumor tissue. In both frontal lobes the tumor tissue is entirely necrotic except for thin rims around the edge. The genu of the corpus callosum was completely filled with and replaced by tumor. The tumor most probably arose in the corpus callosum and extended from it into both frontal lobes. The largest extension was into the left frontal lobe. More posteriorly, the larger amount of tumor was found in the right hemisphere. Tumor tissue was found as far posteriorly as the coronal planes of the mid-thalamus and posterior aspect of the lenticular nucleus.

Histologic examination of this tumor showed it to be a typical glioblastoma multiforme, with pleomorphic cells of which the best differentiated resembled fibrous astrocytes. There were many areas of necrosis throughout the tumor. It seems very likely that the improvement in symptomatology in this case may have been the result of sudden bilateral extensive necrosis in the tumor masses themselves.

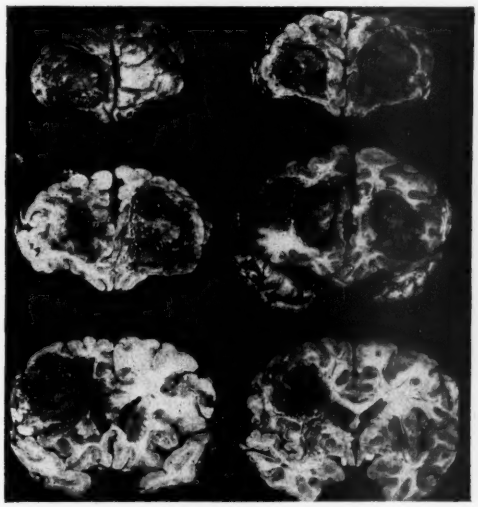

FIGURE 1.

DR. CASTLEMAN: Have we had a tumor as large as this before?

DR. RICHARDSON: We have had them as large, but I do not think we have had as large a tumor in which there was such extensive necrosis.

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ADDRESS OF DR. CLINE

THE farewell address of President John W. Cline to the House of Delegates of the American Medical Association in June contained matter of continuing interest to physicians. Many of the problems that will undoubtedly face the medical profession for years to come were carefully considered, and progress toward their eventual solution was reviewed. Dr. Cline re-enumerated the primary goals not only of the Association but also of doctors everywhere: the determination to extend adequate medical care to more people and to ensure that medical practice retain its present high standards, achieved without outside interference.

Significant progress has been demonstrated in the ability of the medical profession to cope with a fundamental challenge. Until recently, young, well trained physicians found little to interest them in rural communities far removed from the centers of hospital practice and research: neither the financial rewards nor the opportunities for keeping abreast of clinical and experimental advances were sufficient to tempt a young physician faced with the necessity of earning his living and retaining the skills achieved through so much labor in the years of medical school and internship. Dr. Cline cited the fact that young practitioners of medicine are more and more being prompted to settle in rural areas; the activities of medical schools, state societies and the American Medical Association, together with increased interest of local communities in providing adequate medical care, have been mainly responsible for a step toward the solution of what at one time promised to be a serious social problem. The efforts of placement agencies of the state and national organizations have materially furthered the location of physicians in smaller communities, which have themselves helped the situation by improving facilities for practice and providing adequate educational opportunities for children.

The extension of voluntary medical care plans continues to offer hope to those who reject the idea that the national government should provide such protection by means of compulsory health insurance supported by taxation. More than 85,000,000 Americans now have Blue Cross or other hospital coverage; 65,000,000 have surgical and 28,000,000 both medical and surgical protection. Ever-wider extension of the opportunities of voluntary insurance programs continues to be the greatest bulwark against socialization of medical practice. Further progress in this direction is necessary, but as Dr. Cline pointed out in his address, medical leaders have recognized and accepted the responsibility not only of providing medical care of continuously improving quality but also of making it more easily available to all.

To aid in the solution of another problem — that of eliminating the stigma of cultism from osteopathy — and to reduce emphasis on the teaching of osteopathy in favor of instruction in medicine

and surgery, Dr. Cline offered the following recommendation: "that the AMA Council on Medical Education and Hospitals. . . be permitted to advise schools of osteopathy and . . . facilitate the opportunities of these schools to improve their faculties by removing any barrier of unethical conduct on the part of doctors of medicine who may teach in these schools." (This would in no way alter the conviction that physicians "cannot accept or recognize the basic concept of osteopathy as a valid method of treatment of disease" but would offer the co-operation of doctors to representatives of the osteopathic profession who are sincere in their desire to improve the education of students in osteopathic schools.)

Of special interest in the address was the emphasis on continued good relations with the public, which depend largely on the actions of every member of the medical profession. In forthright terms Dr. Cline urged that those who transgress the Code of Ethics "be thrust from the company of gentlemen," thereby demonstrating to the public that conscientious physicians do not tolerate dishonesty or unethical conduct. He outlined the following procedure to keep the public convinced that the profession deserves its respect and support:

> Grievance committees have gone a long way in improving the situation but the mere existence of such committees is not enough. They must be composed of physicians who are respected, not only for their professional attainments but, also, for their character, impartiality and courage. These committees must be active, easily available and the public must be informed of them and the means of access to them.

Finally, in no uncertain terms, Dr. Cline delineated the Association's stand against any attempt at governmental interference with private practice, adding a word of caution against the complacent belief that, in a period of comparative quiet, the proponents of government-guaranteed medical care have abandoned their attempt to regiment medical and hospital practice. He urged upon physicians constant vigilance and unceasing efforts to preserve their independence and that of their patients.

The sentiments voiced by Dr. Cline represent those of most American physicians, as well as of the organization that speaks for them. The address should also inspire confidence in the leaders of the medical profession: so long as physicians and patients continue to be represented by men who have so convincingly demonstrated their capacity for leadership, no efforts at regimentation can prevail. Even more important, doctors and patients alike can rest assured that the progress in medicine already attained will be continued and even surpassed.

ERYTHROMYCIN, NEW AND PROMISING ANTIBIOTIC

THE great increase in incidence of sulfonamide-resistant strains of gonococcus following the widespread use of sulfonamide therapy for gonorrhea, the occurrence of extensive and serious epidemics of infections with sulfonamide-resistant strains of hemolytic streptococci during the program of mass chemoprophylaxis in some of the armed forces during World War II and the increasing prevalence, especially in hospitals, of penicillin-resistant staphylococci have demonstrated that, at least in the field of infectious diseases, one must expect limitations in the effectiveness of the "wonder drugs" as they become extensively used. (That this principle extends beyond the microbiologic field is suggested from the decreasing efficacy of DDT and other chemical insecticides.) In addition, an appreciable number of people have now become sensitized to penicillin, others do not seem to tolerate some of the broad-spectrum antibiotics, and serious toxic effects, such as eighth-nerve damage from streptomycin and aplastic anemias from chloramphenicol, have tended to restrict somewhat the value of these agents.

Partly as a result of these and similar developments and perhaps in greater measure because of the intensely competitive activities of the major manufacturers of pharmaceutical and biologic products in their attempts to capture dominating positions in a lucrative field, extensive surveys and screening programs have been undertaken in many research laboratories in the hope of discovering new antibiotics with desirable, useful and possibly new and unique properties. The present situation in the antibiotic field is analogous to that which existed in the sulfonamide field when tremendous numbers of new derivatives were prepared and studied although few proved to be clinically useful drugs.

The fact that penicillin, the first major product to receive universal acceptance, had such a high activity against a large number of important pathogenic organisms, coupled with a very low toxicity, set an elevated standard for subsequent workers in this field to emulate and surpass. Even from the laboratories of Waksman and his pupils, the great pioneers and most prolific workers in this field, only one widely acceptable agent, streptomycin, has emerged, although they have isolated, described and characterized a formidable list of new antibiotics. And even streptomycin has been limited in its usefulness, in part by its antimicrobial spectrum but even more so by its specific toxic action and because of the rapid emergence of streptomycin-resistant variants during treatment. The British workers under the eminent and stimulating leadership of Fleming, Florey and Raistrick have not as yet provided a single new antibiotic that has proved to be both effective and nontoxic, although they have prepared and characterized a great many active substances.

In this country many groups of workers, by dint of great perseverance, as well as a much greater measure of good fortune, have developed the so-called wide-spectrum antibiotics, chloramphenicol and aureomycin and later terramycin, which is closely related in structure and activity to aureomycin. These three agents have broadened the horizon of antimicrobial therapy by acting against a wider variety of pathogenic bacteria than penicillin and streptomycin, by their greater effectiveness against the lymphogranuloma-venereum-psittacosis group of viruses as compared with the sulfonamides and by their high degree of activity against rickettsial infections, which had been only slightly, though not significantly, affected by earlier antimicrobial agents.

The broad-spectrum antibiotics have gained wide acceptance, but with their extensive use more strains of different organisms are proving to be relatively resistant to one or all of these agents. In addition, some patients have found it difficult to tolerate them, others appear to be sensitive to them, and certain serious toxic effects and the emergence of resistant variants have served as deterrents to the unrestricted use of certain antibiotics, as noted above. As a result, the search for new antimicrobial agents among both antibiotics and synthetic chemicals continues unabated. The isonicotinic acid derivatives have thus emerged as potentially active against tuberculosis and many other antibiotics are now under investigation, some of which give promise of clinical usefulness.

This issue of the *Journal* contains a report from the Thorndike Memorial Laboratory on a new antibiotic — erythromycin. This agent was discovered and some of its properties first described under the trade name "Ilotycin" by a group of workers in the Lilly Research Laboratories.[1] According to those workers, the new antibiotic, which is derived from a strain of *Streptomyces erythreus* (Waksman), is of low toxicity and is active against gram-positive and gram-negative bacteria, mycobacteria, typhus rickettsias and certain large viruses. In preliminary clinical trials this antibiotic has proved effective against hemolytic-streptococcus and pneumococcal infections. Evidence of its value in other human infections has not yet been presented by these investigators.

The workers at the Boston City Hospital have confirmed the favorable clinical effects on pneumococcal and hemolytic-streptococcus infections. They have also shown that strains of *Staphylococcus aureus* tested, including some that are sensitive and others that are highly resistant to other antibiotics, are initially sensitive to low concentrations of erythromycin. In the treatment of a small number of cases of staphylococcal infections the results have been variable so that the hope that this new agent would be the answer to the vexing problem of staphylococcal infections has been only partially fulfilled. Moreover, the high degree of resistance of gram-negative bacillary organisms — the coliform, proteus and pyocyaneus groups — indicates that this agent will have only limited if any usefulness in the management of serious and troublesome urinary-tract infections or even in chronic respiratory-tract infections with these organisms that have proved resistant to the presently available agents. Finally, the rapidity with which high degrees of resistance in strains of staphylococci and of some other organisms have been induced in vitro indicates that, like workers with isoniazid in tuberculosis, the clinician and laboratory worker using this new antibiotic

will have to watch for the emergence of resistant variants and seek possible methods of delaying or preventing its occurrence. That this is more than a theoretical possibility has already been demonstrated by the increase in resistance of the organisms in the blood stream in 2 cases of staphylococcal endocarditis, each associated with clinical failure.

A similar experience was recorded in a case of subacute bacterial endocarditis due to *Str. mitis*, which is included in a group of 10 cases reported by workers at the Mayo Clinic.[2] Favorable results, however, were obtained in other cases of staphylococcal and streptococcal infections, including a case of staphylococcal septicemia and one of subacute bacterial endocarditis due to *Str. salivarius*, but erythromycin failed to sterilize the blood stream in another case due to *Str. faecalis*.

An editorial[3] that accompanies the announcement of the discovery of erythromycin has labeled it "a new broad-spectrum antibiotic." Strictly speaking, this is a correct and proper label because of the wide variety of micro-organisms against which it appears to be active, but it may prove misleading to practicing physicians. It remains to be seen whether the spectrum of erythromycin will prove to be as broad in its clinical activity as that of the agents now recognized by most physicians under the designation of broad-spectrum antibiotics — namely, aureomycin, chloramphenicol and terramycin — or whether, like penicillin and streptomycin, it will be more limited in its area of clinical usefulness. Both these antibiotics are also, strictly speaking, broad-spectrum antibiotics, but they are not recognized as such by the clinician who uses them in the treatment of infectious diseases.

References

1. McGuire, J. M., et al. "Ilotycin": new antibiotic. *Antibiotics & Chemotherapy* 2:281-283, 1952.
2. Heilman, F. D., Herrell, W. E., Wellman, W. E., and Geraci, J. E. Some laboratory and clinical observations on new antibiotic erythromycin (Ilotycin). *Proc. Staff Meet., Mayo Clin.* 27:285-304, 1952.
3. Editorial. Erythromycin: new broad spectrum antibiotic. *Antibiotics & Chemotherapy* 2:279, 1952.

SEASONAL EPIDEMIOLOGY

People who work or play outdoors were warned on July 11 by the information service of a well known life-insurance company "that the summer season, with its sudden and violent thunderstorms, is the period of the greatest danger from lightning."

Not long ago, in order that policyholders might be saved from the unpleasant effects of falling from windows, they were reminded that this particular mishap occurs most often in those seasons when windows are being leaned out of, as for the purpose of substituting screens for storm windows and vice versa.

It may be equally pertinent to warn a gay and heedless people that hunting accidents are prone to occur in the fall, during the hunting season, and skating, coasting and skiing accidents when conditions are favorable for those sports.

THE USES OF ANONYMITY

Anonymity may serve various purposes, some of them innocuous if not, indeed, praiseworthy. It may signify an excess of modesty and spring from the generous desire to do good, unheralded. It may apply to the anonymous donor who wishes to give without causing others the embarrassment of an awareness of his goodness; it may mark the method of the philanthropist who finds joy in contemplating the pleasure that he is creating, as a playwright sits among the audience in a darkened theater and surveys the results of his imaginative genius. It may stem from a more selfish if natural desire to hide the magnitude of one's resources.

Anonymity may result from a fear of reprisal when one has revealed the wrongdoing of others, and then represents a defensive attitude toward the consequences of even a well intentioned act.

An unwholesome form of anonymity finds its expression in the unsigned accusatory or threatening letter, or the telephone call by a person of unrevealed identity. At best such communications are discourtesies; at worst they are malicious acts intended to have consequences for which the originator wishes no responsibility. An opinion that is delivered over the signature of any person who has the courage of his convictions is entitled to consideration; the author of the unsigned communication deprives himself of such consideration by the adoption of methods that do not command respect.

So many fatal accidents have of late occurred in the practice of anesthesia, that it is desirable physicians should have all information possible respecting the different agents employed.

Boston M. & S. J., *August 18, 1852*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

ATWOOD — Blanche L. Atwood, M.D., of Brookline, died on July 31. She was in her sixtieth year.

Dr. Atwood received her degree from Tufts College Medical School in 1914. She was a member of the staffs of the New England Hospital for Women and Children and the Massachusetts Women's Hospital and a fellow of the American College of Surgeons and American Medical Association.

She is survived by her husband, her mother and a brother.

HEALD — Charles G. Heald, M.D., of Pepperell, died on February 28. He was in his seventy-eighth year.

Dr. Heald received his degree from New York University College of Medicine in 1899. He was a member of the staffs of Ayer Community Hospital and Memorial and St. Joseph's hospitals in Nashua, New Hampshire.

He is survived by his widow.

SALTER — William T. Salter, M.D., of New Haven, Connecticut, died on July 30. He was in his fifty-first year.

Dr. Salter received his degree from Harvard Medical School in 1925. He was professor of pharmacology at Yale University School of Medicine and was a fellow of the American College of Physicians and the American Medical Association. He was also a member of the Association of American Physicians, American Society of Clinical Investigation, Association for the Study of Internal Secretions and American Psychosomatic Society.

He is survived by his widow and three daughters.

STONE — Arthur K. Stone, M.D., of Framingham, died on July 31. He was in his ninety-first year.

Dr. Stone received his degree from Harvard Medical School in 1888. He was formerly chief of staff of the Good Samaritan Hospital in Boston, a director of the National Tuberculosis Association, treasurer of the Massachusetts Medical Society and secretary-treasurer of the American Clinical and Climatological Association.

He is survived by his widow, a son and a daughter.

CORRESPONDENCE

SUSPENSION OF LICENSES

To the Editor: At the meeting of the Board of Registration in Medicine held December 13, 1951, it was voted to suspend the registration of Dr. Z. Eileen Taylor, 15 Central Street, Winchester, because of ill health.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

To the Editor: At the meeting of the Board of Registration in Medicine held December 13, 1951, it was voted to suspend the registration of Dr. Victor N. Rochette, most recently of Boston, because of ill health.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

To the Editor: At the meeting of the Board of Registration in Medicine held December 13, 1951, it was voted to suspend the registration of Dr. Jackson M. Rice, of Hyannis.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

REVOCATION OF LICENSE

To the Editor: At the meeting of the Board of Registration in Medicine held December 13, 1951, it was voted to revoke the registration of Dr. Luis A. Mendoza, of 220 Commonwealth Avenue, Boston.

ROBERT C. COCHRANE, M.D.
Secretary

State House
Boston

NONCLINICAL NOTES

Dr. Earl H. Dearborn, of Newtonville, has been appointed head of the Department of Pharmacology of Boston University School of Medicine. Dr. Dearborn has been assistant professor of pharmacology at Johns Hopkins University School of Medicine since 1949. He will succeed Dr. George L. Maison, who has been appointed Director of Research and Development at the Riker Laboratories in Los Angeles.

NOTICES

ANNOUNCEMENT

Dr. George W. Morse announces the removal of his office from 475 Commonwealth Avenue to the Brooks Hospital, 227 Summit Avenue, Brookline.

FISKE FUND PRIZE DISSERTATION

The trustees of the Caleb Fiske Fund of the Rhode Island Medical Society announce the following subject for the prize dissertation of 1952: "The Present Status of Anticoagulant Therapy."

For the best dissertation a prize of $200 is offered. Dissertations must be submitted by December 1, 1952, with a motto thereon, and with it a sealed envelope bearing the same motto inscribed on the outside, with the name and address of the author within. The successful author will also agree to read his paper before the Rhode Island Medical Society at its annual meeting on May 7, 1953. Copy must be typewritten, double spaced, and should not exceed 10,000 words. Further information may be obtained from the Rhode Island Medical Society, 106 Francis Street, Providence 3, Rhode Island.

SOCIETY MEETINGS AND CONFERENCES

AUGUST 25–29. American Congress of Physical Medicine. Page 476, issue of March 20.

AUGUST 31–SEPTEMBER 6. Interamerican Congress of Cardiology. Page 522, issue of March 27.

SEPTEMBER 2–5. International College of Surgeons. Page 190, issue of July 31.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies. Mount Washington Hotel, Bretton Woods, New Hampshire.

SEPTEMBER 8–20. First Argentine Congress of Thoracic Surgery. Page 1024, issue of June 26.

SEPTEMBER 9. Springfield Academy of Medicine. Speaker Dr. W. B. Sherman, New York City.

SEPTEMBER 23. Norfolk District Medical Society. Page 190, issue of July 31.

SEPTEMBER 24. Massachusetts Academy of General Practice. Fall meeting. Hotel Statler, Boston.

SEPTEMBER 26–28. Aero Medical Association. Page ix, issue of July 31.

OCTOBER 1. Essex North District Medical Society. Page 226, issue of August 7.

OCTOBER 1–3. Mississippi Valley Medical Society. Seventeenth Annual Meeting. Jefferson Hotel, St. Louis, Missouri.

OCTOBER 1–3. American Medical Writers' Association. Page ix, issue of July 31.

(*Notices concluded on page vi*)

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